Hospital Library 36

The New England Journal of Medicine

Formerly The Boston Medical and Surgical Journal
Established 1828

Volume 224 FEBRUARY 6, 1941 Number 6

SULFANILAMIDE IN THE MANAGEMENT OF ACUTE STREPTOCOCCAL, PARTICULARLY SCARLATINAL, INFECTIONS OF THE UPPER RESPIRATORY TRACT 221
Conrad Wesselhoeft

THE TREATMENT OF PUERPERAL SEPSIS 226
Joseph P. Cohen

THE TREATMENT OF URINARY-TRACT INFECTIONS BY SPECIFIC THERAPY 229
E. Granville Crabtree

TREATMENT OF MENINGOCOCCAL MENINGITIS 234
Edwin H. Place

SKIN MANIFESTATIONS DUE TO SULFANILAMIDE AND ITS DERIVATIVES 237
Arthur M. Greenwood

CRIMINAL ASPECTS OF FAITH HEALING 239
I. H. Rubenstein

MEDICAL PROGRESS: UNCOMMON INFECTIOUS DISEASES IN NEW ENGLAND 242
Chester S. Keefer

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL 248

EDITORIALS
Chemotherapy and Serotherapy of Pneumonia 254
Criminal Aspects of Faith Healing 255

DEPARTMENTS
Medical Eponym 256
Massachusetts Medical Society 256
Correspondence 258
Report of Meeting 260
Notices 261
Book Reviews 263

Owned and Published by the Massachusetts Medical Society

Published weekly in Boston at 8 Fenway. Domestic, $6 per annum, 25c per copy; Canada, $7.04; foreign, $8.52.
Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.
Copyright, 1941, by the Massachusetts Medical Society.

MASSACHUSETTS MEDICAL SOCIETY

OFFICERS AND STANDING COMMITTEES ELECTED BY THE COUNCIL, MAY 21, 1940

PRESIDENT: WALTER G. PHIPPEN, Salem.
VICE-PRESIDENT: FRANK R. OBER, Boston.
SECRETARY *pro tem.*: ROBERT N. NYE, Boston.
TREASURER: CHARLES S. BUTLER, Boston.
ORATOR: A. WARREN STEARNS, Billerica.

Executive Offices, 8 Fenway, Boston. Telephone, Ken. 2094

STANDING COMMITTEES FOR 1940–1941

COMMITTEE ON PUBLICATIONS
F. H. Lahey, *chairman;* R. M. Smith, J. P. O'Hare, Conrad Wesselhoeft, W. B. Breed.

COMMITTEE ON ARRANGEMENTS
E. J. O'Brien, Jr., *chairman;* W. T. O'Halloran, J. A. Halsted, G. P. Sturgis, H. H. Faxon.

COMMITTEE ON ETHICS AND DISCIPLINE
R. L. DeNormandie, *chairman;* R. R. Stratton, W. J. Brickley, A. G. Rice, F. R. Jouett.

COMMITTEE ON MEDICAL EDUCATION AND MEDICAL DIPLOMAS
J. P. Monks, *chairman;* A. W. Stearns, A. R. Gardner, G. D. Henderson, L. S. McKittrick.

COMMITTEE ON STATE AND NATIONAL LEGISLATION
H. C. Marble, *chairman;* D. L. Lionberger, B. F. Conley, C. A. Robinson, E. M. Chapman.

COMMITTEE ON MEMBERSHIP
G. C. Caner, *chairman;* J. E. Fish, H. F. Newton, P. H. Leavitt, A. W. Reggio.

COMMITTEE ON PUBLIC HEALTH
F. P. Denny, *chairman;* Gerald Hoeffel, S. C. Dalrymple, H. L. Lombard, H. F. Day.

COMMITTEE ON MEDICAL DEFENSE
A. W. Allen, *chairman;* E. D. Gardner, F. B. Sweet, W. R. Morrison, Horatio Rogers.

COMMITTEE ON PERMANENT HOME
W. H. Robey, *chairman;* C. G. Mixter, J. M. Birnie, C. S. Butler, E. C. Miller.

COMMITTEE ON FINANCIAL PLANNING AND BUDGET
John Homans, *chairman;* E. L. Hunt, C. F. Wilinsky, E. J. O'Brien, P. P. Johnson.

OFFICERS OF THE SECTIONS FOR 1941

ELECTED BY THE SECTIONS

The street addresses may be obtained from the *Directory of Officers and Fellows*

SECTION OF MEDICINE
Chairman, A. A. Hornor, Boston; *secretary*, C. L. Short, Boston.

SECTION OF SURGERY
Chairman, R. N. Hatt, Springfield; *secretary*, S. J. G. Nowak, Boston.

SECTION OF PEDIATRICS
Chairman, H. L. Higgins, Boston; *secretary*, J. M. Baty, Belmont and Brookline.

SECTION OF OBSTETRICS AND GYNECOLOGY
Chairman, M. P. Eades, Newtonville and Boston; *vice-chairman*, C. J. Duncan, Brookline; *secretary*, R. S. Titus, Boston.

SECTION OF RADIOLOGY AND PHYSIOTHERAPY
Chairman, C. L. Payzant, Boston; *secretary*, J. H. Marks, Boston.

SECTION OF DERMATOLOGY AND SYPHILOLOGY
Chairman, W. P. Boardman, Boston; *secretary*, J. H. Swartz, Boston.

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES

ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR ANNUAL MEETINGS, BETWEEN APRIL 15 AND MAY 15, 1940

The street addresses may be obtained from the *Directory of Officers and Fellows*

BARNSTABLE — *President*, O. S. Simpson, Falmouth; *vice-president*, J. G. Kelley, Pocasset; *secretary*, D. E. Higgins, Cotuit; *treasurer*, H. F. Rowley, Harwich Port; *librarian*, E. E. Hawes, Hyannis.

BERKSHIRE — *President*, J. W. Bunce, North Adams; *vice-president*, W. A. Millet, Pittsfield; *secretary*, G. S. Reynolds, Pittsfield; *treasurer*, C. T. Leslie, Pittsfield.

BRISTOL NORTH — *President*, R. M. Chambers, Taunton; *vice-presidents*, J. A. Reese, Attleboro; *secretary*, W. H. Swift, Taunton; *treasurer*, J. V. Chatigny, Taunton.

BRISTOL SOUTH — *President*, H. E. Perry, New Bedford; *vice-president*, H. P. Sawyer, Fall River; *secretary* and *treasurer*, A. H. Sterns, New Bedford.

ESSEX NORTH — *President*, R. C. Norris, Methuen; *vice-president*, C. W. Bullard, Newburyport; *secretary*, H. R. Kurth, Lawrence; *treasurer*, G. L. Richardson, Haverhill.

ESSEX SOUTH — *President*, Loring Grimes, Swampscott; *vice-president*, F. R. Ireson, Marblehead; *secretary*, J. R. Shaughnessy, Salem; *treasurer*, Andrew Nichols, III, Danvers.

FRANKLIN — *President*, A. H. Wright, Northfield; *vice-president*, A. W. Hayes, Greenfield; *secretary* and *treasurer*, H. L. Craft, Ashfield.

HAMPDEN — *President*, J. B. Bigelow, Holyoke; *vice-president*, G. B. Corcoran, West Springfield; *secretary* and *treasurer*, W. C. Barnes, Springfield.

HAMPSHIRE — *President*, J. M. Murphy, Florence; *vice-president*, Mary P. Snook, Chesterfield; *secretary* and *treasurer*, J. D. Collins, Northampton; *librarian*, Abbie M. O'Keefe, Northampton.

MIDDLESEX EAST — *President*, G. R. Murphy, Melrose; *vice-president*, J. M. Wilcox, Woburn; *secretary*, K. L. Maclachlan, Melrose; *treasurer*, Richard Dutton, Wakefield; *librarian*, J. M. Wilcox, Woburn.

MIDDLESEX NORTH — *President*, W. M. Collins, Lowell; *vice-president*, W. H. Sherman, Lowell; *secretary*, R. L. Drapeau, Lowell; *treasurer*, M. D. Bryant, Lowell; *librarian*, P. J. Meehan, Tewksbury.

MIDDLESEX SOUTH — *President*, Dwight O'Hara, Waltham; *vice-president*, H. F. Day, Cambridge; *secretary*, A. A. Levi, Newton; *treasurer pro tem*, J. H. Townsend, Belmont; *orator*, H. G. Giddings, Newton.

NORFOLK — *President*, F. P. McCarthy, Milton; *vice-president*, S. A. Robins, Roxbury; *secretary*, F. S. Cruickshank, Brookline; *treasurer*, Frederick Reis, Jamaica Plain.

NORFOLK SOUTH — *President*, D. B. Reardon, Quincy; *vice-president*, W. L. Sargent, Quincy; *secretary* and *librarian*, H. H. A. Blyth, Quincy; *treasurer*, F. W. Crawford, Holbrook.

PLYMOUTH — *President*, S. W. Goddard, Brockton; *vice-president*, G. A. Mount, Brockton; *secretary*, R. C. McLeod, Brockton; *treasurer*, A. M. Champ, Brockton; *librarian*, J. H. Weller, State Farm.

SUFFOLK — *President*, A. A. Hornor, Boston; *vice-president*, J. P. O'Hare, Boston; *secretary*, M. H. Clifford, Boston; *treasurer*, W. T. S. Thorndike, Boston.

WORCESTER — *President*, J. M. Melick, Worcester; *vice-president*, R. S. Perkins, Worcester; *secretary*, G. C. Tully, Worcester; *treasurer*, E. P. Disbrow, Worcester; *librarian emeritus*, A. C. Getchell, Worcester.

WORCESTER NORTH — *President*, B. P. Sweeney, Leominster; *vice-president*, H. C. Arey, Gardner; *secretary*, E. A. Adams, Fitchburg; *treasurer*, F. H. Thompson, Jr., Fitchburg.

The New England
Journal of Medicine

Copyright, 1941, by the Massachusetts Medical Society

VOLUME 224 FEBRUARY 6, 1941 NUMBER 6

SYMPOSIUM ON SULFANILAMIDE AND ITS DERIVATIVES

SULFANILAMIDE IN THE MANAGEMENT OF ACUTE STREPTOCOCCAL, PARTICULARLY SCARLATINAL, INFECTIONS OF THE UPPER RESPIRATORY TRACT*

CONRAD WESSELHOEFT, M.D.†

BOSTON

IN discussing the use of sulfanilamide in streptococcal infections of the upper respiratory tract, it is essential to keep in mind that certain factors influence the natural course of these infections and the efficacy of the drug, and that such controlled clinical investigations as have been made serve merely as preliminary tests, which gauge the value of the drug only under limited conditions in a complex field. Naturally, these considerations lead to generalities, often of a hypothetical and speculative nature, from which diverse opinions are evolved.

Among these upper respiratory infections of streptococcal origin, scarlet fever offers one suitable avenue of approach because of the vast amount of basic statistical material to work from. This disease in a two-year-old child will give rise to an otitis media in almost 50 per cent of the cases, but the susceptibility of the middle ear in this disease decreases as one grows older, until in adults it occurs in only about 5 per cent. This complication varies not only according to age, but also according to the anatomic peculiarities of the patient, the season of the year, the presence of mixed infections,[1] the strain of hemolytic streptococcus obtained from nose and throat cultures[2] and the various little-known influences connected with the patient's environment. Similar factors pertain to the incidence of the other complications of this disease.

It must be clearly understood that these scarlet-fever strains can produce pharyngitis, tonsillitis, lymphadenitis and all the other complications without producing a rash, provided that the patient can neutralize the toxin. Furthermore, other strains of streptococci — not of the scarlet-fever order — can give rise to a similar pharyngitis and tonsillitis with fever in all grades of severity, and to the complications that accompany and follow scarlet fever.

In their superficial growth, these various streptococci may call forth a thin layer of fibrin and may also cause marked localized edema. But their invasive power actually governs not only the severity of the local symptoms in and about the throat, but also the incidence of accompanying and subsequent complications. They can induce a mucopurulent discharge from the mucous membrane, especially in the middle ear, the mastoid cells, the nose and its accessory sinuses. In all these positions there is a constant effort of the resisting forces to protect the underlying structure from the streptococci. However, the bacteria may penetrate still deeper and may seriously invade the lymphatics or bone itself, and thus may reach the blood or the meninges.

How does sulfanilamide influence these upper respiratory conditions? Various factors affect its ability to inhibit the growth of hemolytic streptococci. As a class, these bacteria are among the most susceptible to this drug. Nevertheless, certain strains are more susceptible than others.[3, 4] Furthermore, one is not always dealing with a pure strain. Frequently there are mixed infections in which one strain may supersede another in its preponderance of growth. The tissue involved, the tissue reaction invoked by the infection, and the depth of invasion are of the utmost importance. Indeed, the efforts of the natural resisting forces to wall off and localize the infection may also act to prevent sulfanilamide from getting at the streptococci flourishing within the wall. But it is not only in abscess formation that this walling-off takes place, because fibrin thrown

*This and the following four papers were presented as a symposium at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1940.

From the Haynes Memorial Hospital, Massachusetts Memorial Hospitals, and the Department of Pediatrics, Harvard Medical School.

†Clinical professor of communicable diseases, Harvard School of Public Health; associate professor of theory and practice, Boston University School of Medicine; physician-in-chief, Haynes Memorial Hospital, Massachusetts Memorial Hospitals.

into and on the surface of the mucous membrane of the upper respiratory tract and the relatively impotent superficial phagocytic cells may protect streptococci flourishing near the surface and in the semifluid on the surface. Especially is this true in certain forms of purulent rhinitis. Thus one is confronted with different problems brought about by the elaboration of the toxin on the one hand, and pyogenic properties on the other.

Ordinarily, the initial invasion of the scarlet-fever infection is a superficial one. The rash is a remote effect of the circulating toxin on the skin capillaries, whereas in erysipelas the skin lesion is the direct result of the streptococci within the tissue fluids in the deeper layers of the skin itself. Consequently, sulfanilamide, or the form in which it operates, encounters more difficulty in reaching the superficial lesions of the upper respiratory tract in scarlet fever than it does in affecting the deep skin lesions of erysipelas. Therefore, one should not expect, nor does one obtain, parallel results in the two diseases from the administration of this drug.

Scarlet fever offers an excellent opportunity to investigate the action of sulfanilamide. Given as a routine by mouth throughout the febrile stage in the accepted dosage,* this drug has failed to benefit in any way the eruptive stage in eight clinical studies,[5–12] comprising a total of 1239 cases tested against 1220 controls. One of these studies was conducted at the Haynes Memorial Hospital, the results of which conformed with the others in this respect: the fever was neither lowered nor shortened, nor was any improvement noted in the rash or sore throat that could be attributed to the drug, as determined by a comparison with the control series.

Tonsillitis is a usual manifestation of the initial stage of scarlet fever, and in our series it showed no apparent improvement as the result of the usual dosage of the drug. Why, then, should the non-scarlatinal forms of pharyngitis and tonsillitis be expected to yield to this or to smaller doses? A controlled study failed to show that they do.[13] Both types of tonsillar disease represent invasion, and the only difference lies in the local toxic effects in scarlet fever.

However, if scarlet-fever antitoxin or convalescent serum is administered within the first twenty-four hours, one usually obtains a dramatic drop in the fever, a blanching of the rash and a distinct improvement in the inflamed throat. Here the improvement in the condition of the throat is due to neutralization of the erythrogenic toxin and indirectly to a checking of the bacterial invasion. Thus one can control the toxic stage by the early use of antiserums, which will lower the incidence of complications during the first week to an appreciable degree. But scarlet-fever antiserums exert no more effect on the pyogenic complications, once they have become established, than sulfanilamide exerts on the initial toxic stage.

The next question is whether sulfanilamide can prevent these pyogenic complications. In four of these clinical tests the drug was continued only during the febrile stage. The combined results of the tests[5–7, 9] (474 treated cases, 587 controls) showed no diminution in the incidence of complications. Furthermore, in England,[9, 10] a combination of the drug with scarlet-fever antitoxin was used in 317 cases and controlled by 329 cases in similar age groups treated with antitoxin alone. Again no diminution of the complications occurred as a result of the sulfanilamide, in spite of this additional antibody supply. On the other hand, Benn[11] and Silverman[12] showed a moderate reduction in the pyogenic complications among their drug-treated cases. All these clinical observations are of necessity unsatisfactory and incomplete, since the results always suggest some other approach in the manner of administering the drug, if not some newer allied preparation.

In a series of 350 cases reported by Thenebe and his associates[14] at Hartford, — in which the usual dosage was given on the first day, reduced over a period of the next three days, and then maintained at half the original dose for another four days, — a low percentage of complications occurred as compared with that in previous years, but a very high percentage of toxic effects from the drug was recorded.

In another series — that of Sako and his associates[8] in Minneapolis — the drug was used without antitoxin and was continued on an average of twelve days. Here a very marked diminution in the incidence of complications was reported in the drug-treated cases. The authors remark that "the best results were obtained when sulfanilamide was continued during the entire convalescent period," but they fail to state how many were so treated and what their ages were.

All the complications of scarlet fever may occur at any time during the course of the disease. Schick,[15] years ago, drew attention to the "second danger period," extending into the third or the fourth week. The continued use of sulfanilamide over a three or four weeks' period brings up the question of the dangers from its use, especially in the home. Cases so treated would certainly require closer supervision, with frequent blood counts, and thus add to the cost of medical care. This, of course, would be well worth while if complications could be avoided or reduced to the minimum obtained in the Minneapolis series.

*Sixty to 90 gr. daily by mouth was used for full-grown patients, with proportional reductions according to weight down to 20 to 40 gr. daily.

From a practical standpoint it means hospitalization of all cases of scarlet fever, a reversal of the present tendency toward isolation in the home.

Jewell[16] has recently reported on the use of small doses of sulfanilamide (2 to 5 gr. thrice daily) as a prophylactic for scarlet fever. Similar spectacular results were offered sixty years ago in favor of belladonna in this same capacity. The references on the latter subject fill two columns of the *Surgeon General's Catalogue*. The control method of investigation will eventually give the true answer to the prophylactic value of sulfanilamide in this disease, as it did for belladonna.

In other contagious diseases not of streptococcal origin, hemolytic streptococci are, nevertheless, frequently the cause of complications. Thompson and Greenfield[17] used sulfanilamide in measles and whooping cough in the usual dosage, followed by a maintenance dose in carefully controlled age groups. The drug showed no effect whatever on the eruptive phase of measles or on the paroxysmal manifestations of pertussis, but the incidence of bronchopneumonia was reduced in both diseases in the drug-treated series. Furthermore, there was a material reduction in the incidence of otitis media in the 400 cases of measles that were given sulfanilamide, comparable with the results obtained by Sako and his associates in scarlet fever with a maintenance dosage. Here, again, one must weigh the prophylactic value of this continued method with the actual days of illness caused by the drug — by no means a minor item, even in children, in whom it is relatively well tolerated.

Sulfanilamide is exceedingly valuable in reducing the mortality that follows the onset of serious complications. In scarlet fever the majority of the deaths today are due to the end results of pyogenic infections, particularly of the mastoid cells, in which the blood stream or the meninges become invaded. In these two serious complications, bacteremia and meningitis, the death rate has been so markedly reduced as to make me enthusiastic.

As to the use of sulfanilamide in purulent rhinitis, sinusitis and suppurative otitis media, our experience at the Haynes Memorial Hospital is very conflicting. Some cases with and without evidence of septic toxemia appear to have responded, whereas in others the results are disappointing. This experience in scarlet fever corresponds to the conflicting reports in the literature in these same conditions not of scarlatinal origin. Evidence on this point must be carefully sifted before anything beyond impressions can be given.

In 54 cases of suppurative otitis media in the course of scarlet fever we have given sulfanilamide from the onset of the aural discharge in 14 and later in 40. In this preliminary report I can say only that the duration of the discharge and the incidence of mastoid infection requiring surgical intervention have not been reduced below the average. One thing that we have learned is that a mastoiditis may be subdued so far as the purulent aural discharge is concerned; yet bone destruction continues, and precious time has been wasted.[18] Furthermore, the white-cell count and differential count can be distorted by the drug, likewise the x-ray evidence, as pointed out by Law,[19] thus making it more difficult to interpret the true condition of affairs in the mastoid cells.

Different strains of hemolytic streptococci appear to have various predilections for their original attack. For example, it is fairly unusual for the scarlatinal strains to attack the larynx; yet other strains of hemolytic streptococci can bring about an epidemic of croup. Here one may be confronted by a problem in the use of sulfanilamide. I refer to obstructive laryngitis. At the Haynes Memorial Hospital we have seen 3 cases of severe obstructive streptococcal laryngitis which, before admission, were given sulfanilamide to the point of cyanosis, without improvement. Nor were these due to the viridans type of streptococcus, which is known to be resistant to this drug. Cyanosis and signs of fatigue constitute indications for laryngoscopic examination, suction and, if necessary, intubation, or, in extreme danger, for a prompt indirect intubation. Of course, the cyanosis of sulfanilamide would never alone bring one to this step, but in the presence of increasing obstruction it can handicap one's judgment.

Two one-year-old infants with streptococcal laryngitis were recently admitted to the Haynes Memorial Hospital, both with marked funnel-like recessions of the sternum with each inspiration. They did not develop excessive fatigue or cyanosis, and recovered with moist air inhalations alone. Sulfanilamide was not used.

Intubation is a much more serious step here than in diphtheria, owing to the danger of ulceration if the tube is left in place more than forty-eight hours. Intubation, therefore, with a streptococcal infection is a temporary procedure to afford sufficient sleep and rest and a chance to combat dehydration before a tracheotomy, and to supply free air passage during the tracheotomy, which is done under local anesthesia. In spite of advances in the technic and aftercare of tracheotomy, the dangers of bronchopneumonia and tracheal encrustations continue to make this operation a great risk. Any drug that induces cyanosis in the presence of laryngeal obstruction might mislead one into unnecessary operative interference. Sulfathia-

zole, which does not appear to have this drawback, is now under investigation.

In spite of appearing inconsistent because of inferences to be drawn from our experience in scarlet fever and obstructive laryngitis, I am of the opinion that drastic chemotherapy is indicated in any desperate, fulminating, highly toxic infection of the faucial space and trachea suggestive of streptococcal infection before any culture reports are obtained; and if the cultures are positive for hemolytic streptococcus, I should add immunotransfusion. But I am opposed to its indiscriminate use in the minor upper respiratory infections, except those under investigative control.

In the management of the streptococcal infections of the upper respiratory tract one should be aware of the factors that govern the natural course of the disease and those that interfere with the ability of the drug to get at the bacteria, the variations in their susceptibility and the limits, as well as the dangers, of its use. Nor should one neglect all those useful measures that afford relief, comfort and the saving of life. Improvements in chemotherapy may yet fulfill our hopes in the treatment of these upper respiratory streptococcal infections, but much investigation lies ahead. At present the outstanding value of sulfanilamide appears to be in those sequelae of these infections in which the streptococci have penetrated into the blood stream, the meninges or the lungs.

315 Marlboro Street

References

1. Wesselhoeft, C. Factors influencing the incidence and course of otitis media in scarlet fever. *Ann. Int. Med.* **12**:1473-1485, 1938.
2. Gunn, W. and Griffith, F. Bacteriological and clinical study of one hundred cases of scarlet fever. *J. Hyg.* **28**:250-266, 1928.
3. Keefer, C. S. Sulfanilamide: its mode of action and use in the treatment of various infections. *New Eng. J. Med.* **219**:562-571, 1938.
4. Long, P. H. and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds.* 319 pp. New York: Macmillan Co., 1939. P. 126.
5. Peters, B. A. and Havard, R. V. Chemotherapy of streptococcal infections with *p*-benzylamino-benzene-sulphonamide. *Lancet* **1**:1273, 1937.
6. Schwentker, F. F. and Waghelstein, J. A note on the use of sulfanilamide in scarlet fever. *Baltimore Health News* **15**:41-46, 1938.
7. Wesselhoeft, C. and Smith, E. C. The use of sulfanilamide in scarlet fever. *New Eng. J. Med.* **219**:947-953, 1938.
8. Sako, W., Dwan, P. F. and Platou, E. S. Sulfanilamide and serum in the treatment and prophylaxis of scarlet fever. *J. A. M. A.* **111**:995-997, 1938.
9. Peters, B. A., Woodman, D. and Lewis, F. J. W. Chemotherapy in fever hospital practice. *M. Officer* **62**:55-57, 1939.
10. Hogarth, J. C. Para-benzylaminobenzenesulphonamide in the treatment of scarlet fever. *Brit. M. J.* **2**:1160-1162, 1937.
11. Benn, E. C. Sulphanilamide in the treatment of scarlet fever. *Brit. M. J.* **2**:644-646, 1939.
12. Silverman, A. C. Sulfanilamide in the treatment of scarlet fever: need for research point of view. *New York State J. Med.* **40**:317-325, 1940.
13. Rhoads, P. S. and Afremow, M. L. Sulfanilamide in treatment of sore throat due to hemolytic streptococci with controls. *J. A. M. A.* **114**:942, 1940.
14. Thenebe, C. L., Hirshberg, M. S. and Bobrow, A. Three hundred and fifty cases of scarlet fever treated with sulphanilamide and neoprontosil. *J. Conn. M. Soc.* **3**:351-353, 1939.
15. Schick, B. Die Nachkrankheiten des Scharlach. *Jahrb. f. Kinderh.* **65**:132-173, 1907.
16. Jewell, L. E. The use of sulfanilamide as prophylaxis for scarlet fever. *J. A. M. A.* **114**:1478, 1940.
17. Thompson, A. R. and Greenfield, C. R. M. Chemotherapy in measles and whooping cough: prophylaxis and treatment of complications. *Lancet* **2**:991-994, 1938.
18. Maybaum, J. L., Snyder, E. R. and Coleman, L. L. The value of sulfanilamide in otogenous infections: with special reference to its masking effect. *J. A. M. A.* **112**:2589-2592, 1939.
19. Law, F. M. discussion of Rosen, S. Acute mastoiditis masked by sulfanilamide. *Laryngoscope* **49**:1149, 1939.

Discussion

Dr. Gordon Berry, Worcester: The subject of chemotherapy is broad and complex. I know you join with me in wishing that the time would permit a wider development of the theme by so authoritative a speaker as Dr. Wesselhoeft.

It should be remembered that in streptococcal infections a specialized type of membrane is being considered and that each infection invades this membrane in the same way. Through the agencies of local edema, the deposit of a fibrin layer on and in the superficial tissues and the local increase of phagocytic leukocytes, Nature is delaying or preventing the entry and spread of the bacteria, is trying to wall off the process and isolate it. I cannot speak authoritatively about the chemical or pathologic changes that occur, but I can fittingly emphasize the point made here, namely, that sulfanilamide is blood borne, and that the very barriers Nature establishes in its effort to wall off the process automatically inhibit the drug from reaching the infection. Further, if there is central necrosis and pus formation, the pus is beyond the reach of this drug. Here if Nature cannot cure, only mechanical drainage will serve.

Although antiserums markedly inhibit the initial attacks of streptococcal infections, but not the later complications, sulfanilamide, even if started early and energetically and continued in gradually diminishing doses, does not lessen the initial attack, but does lessen the pyogenic complications. Some would question this, and further research is necessary to settle the point.

I shall now discuss ear complications, which are of particular interest to me as an otolaryngologist. In a series of 54 cases of acute suppurative otitis media, the administration of sulfanilamide did not reduce the duration of the discharge or the incidence of mastoiditis requiring surgical intervention. These negative findings are supported by many of my confreres, but are contrary to the reports of those enthusiasts who claim a startling abatement in ear infections from prompt chemotherapy in all cases.

Let me introduce two contrasting reports. The first, in favor of chemotherapy, is through the courtesy of Dr. Mary S. Holmes, the superintendent at Belmont Hospital, where Worcester's acute contagious cases are handled. The material was assembled by her assistant, Dr. Florence H. Knowlton. This hospital makes a routine practice of administering sulfanilamide (1 gr. per pound of body weight) in all scarlet-fever cases. To protect against sensitivity, the drug is continued for only five days unless the severity of the case or secondary complications urge a continuance. What are the results? The scarlet-fever death rate for the preceding ten years was 1.5 per cent. For the two years of sulfanilamide therapy, 840 cases resulted in 5 deaths, a rate of 0.6 per cent. The incidence of acute otitis media for all ages was 6.8 per cent in an untreated series of 1018 cases and 2.5 per cent in a treated series of 827 cases. These figures show a gain of about two and a half times. Mastoidectomy, not infrequent in the untreated series, was a rarity in the treated. In 1935 and 1936 the average hospital stay for scarlet fever with otitis media was 47 days. In 1938, when the drug was used as a routine, the average stay was reduced by a half, to 23 days. The fever and the rash disappeared promptly in most of the treated cases. Antiserum was used in a little less than one quarter of the cases in both series. Dr. Holmes credits these results to the sulfanilamide therapy, and also to the isolation of each case in a separate room, thus avoiding cross infections. In over 1000 cases administered sulfanilamide in this hospital, no serious toxic complications were caused by the drug.

The second report reflects the more conservative attitude of most otologists. Dr. Edmund P. Fowler, Jr.,* has listed the types of organisms found in cultures from aural discharges at the Columbia Presbyterian Medical Center in New York during the last seven years. Such cultures should indicate the primary offending organism. But it must be borne in mind that secondary infections early enter from the nasopharynx or from the skin of the external auditory canal, and that the resulting mixed infection complicates therapy. Sulfanilamide may be helping the streptococcal infection while a complicating staphylococcus is causing serious secondary trouble. The total number of cases in this New York series was 2755. Of these over 35 per cent showed staphylococcus, and more than 15 per cent, other organisms; thus over 50 per cent were not susceptible to any known specific chemotherapy. (Sulfapyridine and sulfathiazole are offered for staphylococcal infections, but they are not yet considered specific remedies.) About 30 per cent of this series showed hemolytic streptococci, for which we have sulfanilamide, and about 15 per cent were due to pneumococci, for which we have sulfapyridine. A second study showed the duration. In a series of 455 cases of acute suppurative otitis media that did not receive chemotherapy, — and a hospital is likely to see the worst forms, — the total duration of the ear discharge in all types of infection was less than one week in 68 cases, less than two weeks in 209, and less than three weeks in 269. Of the 264 cases with pneumococcal and streptococcal infections, including the severe complications, three quarters of the patients got well within three weeks without chemotherapy. Dr. Fowler reasons that acute otitis media is usually a self-limited disease and that too many cures are being attributed to chemotherapy. He thinks a fair estimate of cures by such means, as against former measures, would place the gain at less than 5 per cent. His figures show that less than half the cases of otitis media lend themselves to chemotherapy and that three quarters of this possible half recover about as promptly without the use of the specific drug. He concludes that perhaps one eighth of all cases of acute otitis media need chemotherapy.

In considering infectious processes in this region, one should bear in mind that all these cavities are bony, epithelial-lined air chambers connected with the central airway. The middle ear and mastoid may be thought of as a modified paranasal sinus. An acute nasal cold always involves to a degree the easily accessible ethmoid cells. If it extends through the eustachian tube, the infection involves the mastoid cell membrane almost as soon as that of the tympanum. We shall clarify our reasoning if we accept this early involvement of these contiguous cavities. Treatment may employ belladonna as of old, or the sulfanilamide of today, but locally we must seek and secure drainage of these adjacent cavities. Dr. Wesselhoeft explains why the sulfanilamide will not reach them. To drain the paranasal sinuses, we shrink the turbinates and ostiums; for the middle ear, we shrink the eustachian tube. If the ear fails to gain, then we must seek surgical drainage, through the eardrum, or later through the mastoid cortex.

Up to this point most otologists rarely use chemotherapy. I cannot see the wisdom or logic in using the drug in mild self-limited nasal and aural infections or in a localized suppurative mastoiditis. Why submit a patient, who probably will get well promptly, to such a heavy broadside, with its known dangers? And the drug masks the symptoms, as Dr. Wesselhoeft has pointed out. The fever may drop, the pain and discharge may cease, the drum membrane may heal and the hearing may return, and still one may be forced to operate, finding an active pocket of pus in the mastoid. I insist, therefore, on surgical drainage when I think it is called for. I have almost invariably regretted an undue reliance on chemotherapy. There are two exceptions to this initial postponement of sulfanilamide. One is an acute fulminating streptococcal infection, regardless of its locality; here the infection is breaking through Nature's barriers, and one must call on the reserves at once. The second exception is an acute streptococcal mastoiditis, for which a free myringotomy has been done and which is hanging in the balance. A short intensive course of sulfanilamide therapy, gradually withdrawn, may favorably turn the scale. But its masking effect, in addition to its hazards, must be carefully borne in mind.

One possibility not yet finally evaluated is its local use. Sulfanilamide in powder form can be applied directly to infected surface tissues, or Neoprontysil in solution can be injected into cavities. Some claim good results, others are not certain.

Except for this possible local use and until the experts recommend smaller and safer doses, one should tend to reserve this modern offensive weapon for the major battle. At any point when the infection looks as though it might seriously reach beyond Nature's normal barriers, then call on this reserve, unstintingly. Dr. Fowler accepts a week to ten days of the infection as an arbitrary limit: if the infection is not under control by then, use the drug. This is a helpful rule. Some of us prefer to consider each case individually and call on this help promptly when we think that convalescence is not progressing well. Please note the time limit: seven to ten days. But experts in chemotherapy say that the hazards from drug sensitivity tend to develop from the seventh to the tenth day. Many withdraw the drug then in order to avoid these hazards. This is just the time the otologist begins to need the drug for the severe complications that may develop. The obvious question is, Why use up this valuable aid when one does not need it, and withdraw it at the time when one may sorely need it? The otologist concludes: reserve the drug for these later complications.

I cannot here go into a detailed consideration of the dangers of chemotherapy. We have all experienced them. Although sensitivity develops more frequently from the seventh to the tenth day, it may develop more promptly. And although we are urged to force the drug in massive doses right at the start, small doses as well as large can bring on these unfortunate reactions. The doctor must therefore decide first, whether with a little waiting the patient can get the best of the infection without the drug, and secondly, whether, if he uses the drug, the expected gain is greater than the hazard. And bear in mind that a good many patients whose cures have been attributed to chemotherapy would have recovered anyway.

At the last meeting of the New England Otological and Laryngological Society, Dr. Champ Lyons gave a masterly dissertation on chemotherapy, urging its prompt and energetic use. If the proper and specific drug is available for an acute middle-ear infection, he urges its use right at the start, in heavy doses and with the patient hospitalized, always. If the drug is doing what it should do, the fever will be down and the ear dry within forty-eight hours. But such an intelligent and drastic effort predicates expert laboratory checking not only of the drug content in the blood and its effect on the red and white blood cells, but of the immune bodies present. If these immune bodies are abundant, the drug is less need-

*Fowler, E. P., Jr. Otitis media and its extensions. *Bull. New York Acad. Med.* 16:24-37, 1940.

ed; if they are lacking, he recommends not only chemotherapy but the considered use of antiserums. In such expert hands, chemotherapy becomes an exact science, and its reactions and hazards are known and understood. As yet the average hospital and laboratory enjoys neither the financial resources nor the technical skill for these elaborate procedures in routine practice. And very few patients can afford to call a mild earache a major hospital disease, even though serious complications may be brewing. In the meantime it is to men like Dr. Wesselhoeft and Dr. Lyons that we gratefully look for safe and wise leadership in this remarkable field of chemotherapy.

This brings me to Dr. Wesselhoeft's final point: the use of sulfanilamide in streptococcal extensions from the ear and mastoid, or from the nose and paranasal sinuses, to the meninges or to the blood stream. Here otologists are in complete accord: begin the therapy at the first suspicion of trouble. The patient is in the hospital and has been under observation. The culture report has been made, the blood and kidney condition is known. Now use the drug promptly and in massive doses. Keep the fluid intake down to hasten the blood saturation — 8 mg. per 100 cc. is usually enough, but do not hesitate to go to 12 mg. or even higher. To the otologist who formerly labored frantically but without avail on his meningitis and sinus-thrombosis cases, the results are little short of miraculous. The case is desperate, surely, but the patient now has a good chance of recovery, provided of course that any necessary surgical drainage has first been secured. Here the drug hazard does not weigh in the balance against the great gain to be secured.

The one caution that experience indicates is not to withdraw the drug too soon. I have operated on the mastoid, controlled the meningitis, withdrawn chemotherapy and sent the patient home apparently well, only to have him hurried back to the hospital in a few days with a second attack of frank meningitis. Fortunately, more sulfanilamide is usually successful in bringing about a lasting cure.

One thing we now hope for is a drug that can be used with safety and in small prophylactic doses. We need therapy that can be administered at the office or at the home, and that will control the infection in its initial stages. Until chemical research corrects the known faults and makes laboratory control simpler, otolaryngologists will tend to hold this most valuable agency as a reserve against serious secondary complications. In the meantime, discussions like these will clarify the existing confusion and will help to guide our procedures.

THE TREATMENT OF PUERPERAL SEPSIS*

JOSEPH P. COHEN, M.D.†

BOSTON

THE advance of knowledge in chemotherapy has stimulated interest in the treatment of puerperal sepsis. Despite this, however, it should be kept constantly in mind that the keynote of emphasis should remain the prevention of the disease. The vaginal tract rarely harbors organisms that are productive of serious infections. These organisms are introduced extragenitally. According to Chandler[1] the incidence of Group A strains of the beta-hemolytic streptococcus in the vagina before delivery is 0.25 per cent, yet in patients with severe puerperal infections almost 100 per cent of the strains isolated bacteriologically are in Group A. The treatment of puerperal sepsis, therefore, begins with preventive measures in the prenatal period, continues with rigid adherence to aseptic principles throughout the intra-partum phase and is not concluded until the post-partum period is completed.

Ante partum, patients should be admonished against intravaginal manipulation, particularly in the last month of pregnancy. They should be instructed not to take douches; coitus should be interdicted.

To protect the patient during delivery, the delivery room should not be used for surgical practice, masks should be worn by all attendants, and patients harboring intercurrent infections should be delivered under conditions that ensure isolation. Proper sterilization of the instruments and gloves is fundamental. Persons who are known to have respiratory infections should be kept out of the delivery room, and if the patient herself has a respiratory infection, every precaution should be taken to avoid autoinfection. Patients must be shaved, and scrupulous aseptic technic should be practiced during delivery. Vaginal examinations should be reduced to a minimum during labor, even though they may be conducted with a rigid technic. As a matter of fact, the progress of labor is readily followed under most conditions by rectal examinations. Prior to delivery the patient should be draped with sterile sheets after preparation of the skin and vulva with suitable antiseptics, and the operator scrubbed as if for the most important surgical adventure, for so the simplest obstetric case may turn out to be.

Post partum, all patients are isolated who have a temperature of 101°F. for a period of a few days, particularly when accompanied by chills, elevated pulse, headache, anorexia, and nausea and vomiting. Prompt isolation will reduce the incidence of epidemics. One should rule out engorged breasts, gastrointestinal disorders and known contagious diseases that do not require isolation. Patients who are to be isolated are

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1940.

†Instructor in obstetrics, Harvard Medical School; surgeon-in-chief for gynecology and obstetrics, Boston City Hospital.

placed in a separate ward or building under the charge of nurses who have no responsibilities with other patients. Wards are frequently scoured, fresh linen is given daily to each patient, bedpans are sterilized before they are used, and nurses are taught a rigid technic in the use of antiseptics. Nurses with local or pulmonary infections should be removed from duty. These details of prophylactic care are essential to reduce the spread of puerperal infections and are of prime importance in the treatment and eradication of the disease.

Since devitalized tissues play an important role in creating conditions favorable to the growth of organisms,[2] the attendant must avoid traumatization; his judgment must be good, his skill ingenious. This means early selection of cases for cesarean section, preferably before rupture of the membranes and within twelve hours of the onset of labor. One should adhere to the precepts of delivering patients vaginally only at full dilatation, and when the delivery is instrumental, of employing gentle traction after an intelligent application of forceps. Except in cases of retained placenta or post-partum hemorrhage, the completion of the third stage of labor without intrauterine exploration is vital.

To give intelligent care to an obstetric patient who is septic, that patient should be properly evaluated not only from the evidence furnished by signs and symptoms of the disease but also by bacteriologic and hematologic studies. To clarify diagnosis, to aid in prognosis and to render intelligent therapy one should know what organism or organisms one is dealing with and whether the infection is localized or in the blood stream; therefore, cultures should be taken from the cervix and the uterus, and blood cultures should be obtained early, and repeated if negative. At the same time blood studies are conducted to determine the red-cell and white-cell counts. The streptococcus, staphylococcus, pneumococcus, colon bacillus and gonococcus are the commonest infecting organisms of the genital tract of the parturient woman. The infections that most seriously jeopardize the patient's life are for the most part confined to beta-hemolytic steptococcus. Almost all human strains of the beta category fall into Group A. Other streptococci produce only partial hemolysis, and certain anaerobic types have the vagina as a normal habitat and are not pathogenic.

Since most of the puerperal infections tend to remain localized in the cervix, uterus or parametrium, the uterus should be kept contracted with oxytocics used orally or parenterally. Ergot and pituitary extract are given early post partum and are continued for the first three to five days. Intrauterine procedures such as douches or curettement are contraindicated[2, 3]; they disseminate infection and may prove fatal.

In generalized blood infections, the hemolytic streptococcus acts by invasion and growth in the host and by the elaboration of toxins. The body mechanism employs phagocytosis and intracellular digestion to oppose this growth. The bacteria may develop a protective mechanism — a capsule — that hinders the phagocytic process. Since sulfanilamide, sulfapyridine and sulfathiazole have been found to be bacteriostatic in vitro and in vivo, they have become utilizable in the production of bacteriostasis.

But this is not always enough. It was found that this phagocytic action might be increased by the presence in the blood of a specific antibody that is antibacterial in nature and sensitizes the organism. This specific antibody, termed opsonin, can be evaluated in the laboratory by blood examination. Therefore, in those patients who possess a low opsonic index, the opsonin may be increased by the transfusion of blood from an immune donor or one found to possess a relatively high antibody content. Treatment by means of sulfanilamide in combination with immune transfusions seems ideal. Colebrook and Purdie[4] showed reduction in the total case fatality rate in puerperal sepsis of 62 per cent, whereas the fatality rate in bacteremic cases fell from 75 per cent to 27 per cent after the use of chemotherapy.

To confirm the bacteriologic diagnosis, blood cultures should be taken before the administration of sulfanilamide. Blood cultures taken after therapy has been started are likely to be negative. If so, and if the history and intra-partum experiences indicate that the patient is potentially infected, it is justifiable to employ chemotherapy prophylactically.

Sulfanilamide or one of its derivatives must not be employed without an understanding of the toxic properties and must be administered under strict supervision, so that the drug may be stopped when ill effects become obvious. Long, Bliss and Feinstone[5] noted toxic signs in a series of 307 cases and were impressed with their relative importance. They have listed fever, jaundice, acute hemolytic anemia and agranulocytosis as sufficiently serious to abandon the use of sulfanilamide. At the Boston City Hospital we have found nausea, vomiting and leukopenia common. Cyanosis, although at first a cause for concern, was found later to be no contraindication to the continuance of the sulfanilamide. The occurrence of psychic disturbances has been annoying and severe enough to make it wise to omit the drug

or reduce its dosage. Since sulfanilamide is rapidly excreted by the kidneys, the increased ingestion of water serves to speed up the neutralization and elimination of the drug. Occasionally, when the drug has to be omitted because of its toxicity, it may be resumed after the lapse of a few days, but in smaller doses. It has been our practice to combat the possibility of acidosis by the administration of equal doses of bicarbonate of soda.

Blood observations should be made twice a week to ascertain and maintain the concentration of the drug at a level of 8 to 10 mg. per 100 cc. of blood. This is extremely important to obtain the maximum beneficial effect from the sulfanilamide and at the same time to reduce both the severity and the incidence of toxemia. To maintain a high blood concentration of sulfanilamide it is possible that fluids may have to be reduced so that the daily urinary output is brought to just above 1000 cc. To guard against the development of agranulocytic angina or acute hemolytic anemia, blood studies are made every other day, including red-cell and white-cell counts and hemoglobin determinations. Blood smears should be examined to observe the type of cells.

Although the accepted procedure is to give an initial dose of 5 gr. of sulfanilamide per 10 pounds of body weight, at the Boston City Hospital we have given no more than 40 gr. as the original dose. After that we have given 15 gr. every four hours. Thus most of the patients have received 90 gr. a day, although occasionally they have received 120 and infrequently 180. Blood-level readings should serve as the guide. This was not done routinely.

Although transfusions with the blood of an immune donor are of known and often dramatic benefit to the patient, the transfusions on the maternity wards at the Boston City Hospital were from donors who were merely found to be compatible. As such, the transfusions were used with indifferent success in some very severe cases, whereas in others the results were surprisingly effective. From 250 to 500 cc. of blood was employed at a time. One or two transfusions were usually given, but occasionally six or seven at three-day intervals.

Recently sulfapyridine has been employed on the maternity wards. In vitro sulfapyridine is said to be bacteriostatic in considerably higher dilutions than sulfanilamide. Sulfapyridine, although more rapidly absorbed than sulfanilamide, is less rapidly excreted. We administer 15 gr. every four hours until signs and symptoms subside. However, recent studies by Brown, Thornton and Wilson[6] have shown that sulfapyridine is more toxic than sulfanilamide. They have noted oliguria, hematuria and costovertebral pain twice as frequently with the former as with the latter. We have not observed these reactions. Nearly all their cases dealt with pulmonary infections.

In the three-year period from 1937 through 1939 9691 cases were delivered at the Boston City Hospital. There were 49 septic cases, 25 of which were delivered normally; 4 were fatal. Five cases had blood cultures positive for hemolytic streptococcus.

Sulfanilamide was employed in the form of Prontylin in 36 cases. Eleven of these cases had, in addition to sulfanilamide, transfusions of citrated whole blood; usually 500 cc. of blood was given. Five of these 11 cases showed a sharp drop in the fever within forty-eight hours.

Of the 4 fatal cases, 1 was given sulfanilamide for twelve days, that is, from the seventh to the nineteenth day post partum, with sulfapyridine for an additional two days. There was no obvious beneficial effect from the drug. However, only 40 to 80 gr. of sulfanilamide was used daily. The patient died in six weeks of subacute bacterial endocarditis. Hemolytic streptococci were recovered from the blood. The patient was delivered normally. She was not transfused. The levels of sulfanilamide concentration in the blood were not determined.

The second fatal case was delivered by low forceps. The patient developed thrombophlebitis and began running a fever on the eighth postpartum day. On the ninth day she was started on Prontylin and given 60 to 90 gr. a day for seven days. She died on the nineteenth day. The diagnosis of septicemia on the record was not confirmed by blood culture.

The third case, following a normal delivery, ran a temperature of 100 to 100.5°F. for five days, with a subsequent rise to 104. Blood cultures were reported negative. She was given Prontylin, 90 to 120 gr. a day, from the eighth to the tenth day, then 60 gr. daily until the twenty-sixth day, when she died. Nine transfusions of 400 to 450 cc. of blood were given.

The last case was a normal delivery of a premature fetus. The patient had pyelitis before delivery. There was a history of nephrectomy for stone two years previously. The temperature swung from 101 to 105.2°F. A hemolytic streptococcus was recovered from the blood. The patient was given 500 cc. of blood on the thirteenth, fourteenth and sixteenth days and Prontylin, 60 to 120 gr. a day, for ten days. She died on the seventeenth day.

Summary

It is apparent that although sulfanilamide is a valuable addition to our armamentarium in the treatment of puerperal sepsis, it must not be relied on completely. Deaths from these infections continue to occur. The fact that 25 of the 49 septic cases were delivered normally shows that instrumentation per se is not so heavily responsible as is believed and that infection may arise under the simplest conditions at delivery. Transfusions, although known immune donors were not used, are supportive and should be carried out in severely septic cases. Transfusion with the blood of an immune donor has been shown to be of immense value. Despite the evidence of all known benefits from the use of various forms of therapy, the greatest reliance must be placed on prophylaxis for the reduction of the incidence of infection.

466 Commonwealth Avenue

References

1. Chandler, C. A. Sulfanilamide in treatment of postabortive and puerperal streptococcal infections. *M. Clin. North America* **23**:1231-1243, 1939.
2. Colebrook, L. Prevention of puerperal sepsis. *J. Obst. & Gynaec. Brit. Emp.* **43**:691-714, 1936.
3. Mengert, W. F. Puerperal sepsis. *Journal-Lancet* **58**:517-523, 1938.
4. Colebrook, L. and Purdie, A. W. Treatment of one hundred and six cases of puerperal fever by sulphanilamide. *Lancet* **2**:1237-1242, 1291-1293, 1937.
5. Long, P. H., Bliss, E. A. and Feinstone, W. H. Mode of action, clinical use and toxic manifestations of sulfanilamide; further observations. *J. A. M. A.* **112**:115-121, 1939.
6. Brown, W. H., Thornton, W. B. and Wilson, J. S. An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine. *J. A. M. A.* **114**:1605-1611, 1940.

THE TREATMENT OF URINARY-TRACT INFECTIONS BY SPECIFIC THERAPY*

A Clinical Discussion

E. Granville Crabtree, M.D.†

BOSTON

THE treatment of urinary-tract infections has recently passed from the stage of administration of a group of comparatively harmless and, for the most part, inefficient drugs, to the use of a group of potent but potentially harmful chemicals.

The term "specific," when applied to these antiseptics, is not easily defined. It certainly does not suggest that the drugs are not suitable for treatment of other than urinary-tract infections. The implication that there is a certain drug that should be administered in, for example, colon-bacillus infections of the kidneys and bladder, to the exclusion of all others, is not in accordance with clinical facts. Perhaps we mean that specific drugs are potent drugs. Without question some of the newer chemicals are potent. Some of them are more suitable than others in the treatment of the pyogenic bacteria that are concerned in urinary-tract infections. In this respect they approximate the accepted use of the term specific drugs. There are also abundant examples of failure to obtain cure of infections even after serial administration of first one, and then another, of these potent antiseptics. Let us then consider specific urinary antiseptics to be more potent drugs than those to which we have been accustomed, with sharp differentiation as to action in acid and alkaline urines — some of them showing superior qualities for sterilization of channels infected with certain types of bacteria, but all limited in effectiveness by certain diseases of the urinary tract and by its physiology.

The development of the now considerable group of new urinary antiseptics has demanded a more scientific attitude on the part of the dispenser than the older drugs required. The cost of these drugs is greater. Some physicians hesitate to administer certain of them outside the hospital, which adds to the economic factor. To aid in the choice of antiseptic, the bacteriology of the infection should be known, and there is always the menace of renal injury from mandelic acid, and both renal and systemic injury from drugs of the sulfanilamide group. It may fairly be assumed that the practitioner is well acquainted with the properties of these drugs and their administration; however, if one may judge from his use of them, he has not yet caught up with the problems of renal physiology on which their successful use in complicated cases depends, and is not fully aware of the significance of disease of the urinary tract in relation to possibilities of cure.

I shall not attempt to discuss the various forms in which mandelic acid and the sulfanilamide groups of drugs are obtainable, or the virtues of each form. The literature is voluminous on these phases of the subject. Most of us have read it.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1940.

†Chief of the Department of Urology, Beth Israel Hospital; visiting urologist, Boston Lying-in Hospital.

Acute Infection of the Urinary Tract

Acute infections of the urinary tract show a marked tendency toward involvement of the whole tract, including the prostate in men, when the extent of the involvement is determined by cystoscopic studies rather than by symptomatology. Acute infection of the kidney is pyelonephritis when fever is present.

The acutely infected patient presents not only the question of how best to render the urinary tract sterile, but also the problem of clearing pus from the kidney and of controlling the toxic effects of the infection on the patient, which are manifested in nausea, vomiting, anorexia, dehydration and, if sufficiently long continued, anemia. The severity and duration of the chronic stage of infection often depend on the management of the acute stage of the disease.

I now make use of forced fluids, by whatever means, and alkalinization of the patient's urine as the first stage of treatment. When this has been accomplished for from twelve to twenty-four hours, even though the fever continues, the patient can maintain an intake of fluid at from 3500 to 5000 cc. and can manage a supporting diet adequate to prevent the development of anemia. Antiseptics can then be administered and will be tolerated.

I prefer to use sulfanilamide drugs rather than mandelic acid in treating the acute stage of urinary infections. The preliminary treatment already advocated is aimed at the control of acidosis, and any form of acidification therapy bids for a return to that condition. Dosages of sulfanilamide need not be so large as those commonly given for some other diseases. Forty grains a day, in divided doses over a period of six to seven days, is usually adequate. The blood level produced by sulfanilamide may reach only 2.5 to 6.0 mg. per 100 cc. Sixty grains daily has been required for a few cases. The change to higher dosage will be indicated by the third or fourth day, if it is noted that adequate progress is not being made. On the whole, a patient who is being benefited by the drug will demonstrate a fair degree of improvement by the third or fourth day of treatment. If some signs of clearing of the urine are not apparent, or if it appears to clear and then clouds again during treatment, sterilization of the urine probably cannot be accomplished at this time. Return of temperature to normal will have been accomplished in most cases even though a clearing of the urine has not been obtained. If the patient is alkalinized before therapy is begun, cases of intolerance to the drug will be less common. The prostatitis that frequently accompanies urinary-tract infection is less likely than the urinary-tract infection to be cured by sulfanilamide therapy, and may persist and give rise to recurrent infection at some remote period. One will do well to test for prostatitis by massage at the end of treatment of an acute infection in men.

There is always the possibility that there is some form of obstructive lesion in the urinary channels in any case of acute infection. The presence of such a lesion cannot be determined cystoscopically with safety in these cases, since cystoscopy often causes severe damage when done in the course of an acute condition. It is safest in pregnancy and exacerbations of chronic conditions. The history will usually give sufficient indication of a chronic condition, and intravenous pyelography will usually detect an acute obstruction, such as a stone, since sufficient function usually remains in the kidneys, in spite of the pyelonephritis, to secrete the dye.

Subacute and Chronic Infections of the Urinary Tract

Subacute and chronic infections offer a wider choice of antiseptic drugs than the acute infections do. They also allow time for adequate diagnosis of the condition of the patient, the presence or absence of gross pathologic conditions, and the estimation of the function of the kidneys, both together and as individual organs. It is in this group of infected cases that renal deficiencies are common and gross pathologic conditions, which are often the result of the infections, are encountered. Total renal function is often low, and uremia may be present.

There is a place for mild antiseptic medicines in subacute cases. I make use of hexamethylenamine, without reduction in intake of fluids, for immediate postoperative treatment of residual infection. Doses of 7½ gr. four times daily will prove adequate for clearing many of these infections. It can be safely administered to ambulatory patients. The drug should be confined almost entirely to the treatment of the common infections due to the gram-negative bacilli and acts best at pH 5.3 or below. Increased irritability of the bladder and blood in the urine are the only contraindications to its continued use. These signs and symptoms usually quickly disappear on withdrawal of the medication.

Mandelic acid is also applicable for the treatment of ambulatory patients who have chronic infections. And it is useful for treating some patients who do not tolerate sulfanilamide, although I consider the drug on the whole less effective as an antiseptic, both because of its limited range

in the bacterial field and because it requires a strong acidifier.

Routine administration of a fixed amount of acidifier with mandelic acid is undesirable. Some patients do not need any acidifier at all; some may need it at the beginning of the treatment and then either part or all of it may be withdrawn. Routine use of the acidifier, when the urine is already strongly acid, only hastens signs of renal irritation in some cases, and forces discontinuance of the treatment, which might have been carried to completion under less acidification. Attention to the acidifier by daily pH determinations is the most satisfactory method of administering the drug. Some urines cannot be acidified, because of the urea-splitting bacteria that they contain, no matter how much acidifier is administered. It must be remembered that only the urine is alkaline, and that serious degrees of acidosis may result if the acidifier is pushed in cases that continue to exhibit alkaline urine. When dangerous degrees of acidosis are so produced, the intravenous administration of a 2 per cent solution of sodium bicarbonate is indicated. About forty-eight hours after beginning mandelic acid therapy a fairly stable, low pH is established and remains almost constant, without the usual alkaline flood at mealtime or the other fluctuations noticeable in a normal person.

The sulfanilamide drugs are my choice of treatment for most of the long-standing infections. This is particularly true when the patients can be hospitalized. They are very effectively used during the latter portion of a patient's convalescence in the hospital, when chronic infections are treated after removal of stone or after correction of renal lesions. The amount of drug required is similar to the dosage for acute infections. The staphylococci yield to sulfathiazole more readily than to other drugs of this group, although as yet experience with it has not been so extensive as with sulfanilamide.

Unjustifiable Uses of Specific Urinary-Tract Antiseptics

Sufficient experience with specific urinary-tract antiseptics has been accumulated to make possible the enumeration of a considerable group of conditions in which their use can be expected to fail to produce a cure. It is proper to call attention to these cases because it is apparent that extensive courses of treatment are often given, with loss of time, considerable expense and no benefit. Table 1 lists 50 consecutive cases in which much unprofitable treatment was given. These cases all exhibited urinary-tract infection. The primary conditions that underlay the infection are given. These cases emphasize what appears to be a fact; namely, it is seldom wise to continue to treat chronic infections without sufficiently complete diagnosis to indicate the presence or absence of gross disease, and something of the function of the kidneys. It is to be noted that 21 cases were presumably cured after diagnosis and remedial measures had been employed. Five, however, recurred after apparent cure had taken place.

One can state with some confidence that antisepsis can be expected to fail when stasis of urine exists anywhere in the urinary tract. It is recognized that small degrees of stasis in the ureters, pelves or bladder are not of sufficient importance to negate treatment. For the bladder, a residual urine of 3 ounces probably represents the upper limit. Much smaller amounts of stagnant urine are effective in interfering with treatment when they occur in the pelves and ureters.

Table 1. *Diagnosis in 50 Cases in Which Specific Drug Therapy Failed.*

Diagnosis	No. of Cases	No. of Cured Cases	No. of Recurred Cases
Chronic pyelonephritis	5	1	
Prostatic obstruction (residuals 5 to 53 ounces)	5	2	
Renal abnormalities	5	4	
Infection due to staphylococci, *Proteus vulgaris* or *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*)	3		
Prostatitis, with urinary infection	3		
Bladder tumor	3	2	
Debility	4	3	1
Diverticulosis of sigmoid	2		2
Contracted kidneys	2	1	
Renal calculus	2	2	
Post-partum pyelonephritis	2	1	1
Hypertension, with inability to concentrate urine	3	1	
Gonococcal prostatitis	1		
Gonococcal prostatic abscess	1		
Abscess of Bartholin's gland	1	1	
Tuberculous perforation of bladder	1		
Old poliomyelitis, with bladder residual	1		
Cystocele	1	1	
Carcinoma of sigmoid, hydronephrosis	1	1	
Nonfunctioning kidney	1		
Cyst of broad ligament, hydronephrosis	1		1
Multiple abscesses of kidney	1	1	
Stricture of urethra, with diverticulum	1		
Totals	50	21	5

The presence of the drainage does not prevent the tissue effect of sulfanilamide from taking place, as evidenced by subsidence of temperature, but does prevent the production of sterile urine.

Cases on constant drainage offer little chance for sterilizing the urine so long as the drain is kept in place. This is particularly applicable to prostatic hypertrophy and its surgical treatment.

Stones, large tumors of the bladder and extrinsic conditions that either involve the urinary organs or by encroachment produce abnormal physiologic behavior of the urinary channels are almost certain to interfere with the cure of urinary-tract infections.

Antiseptics cannot be expected to reach closed pus or partially obstructed pus-containing organs in sufficient concentration to clear infection. This group should include abscesses, pyonephrosis, infections of Skene's or Bartholin's gland, prostatitis and perinephritis. Since urinary-tract infections are common in prostatitis and accessory lymph-node infections, recurrence of the urinary-tract infection is, in a large measure, dependent on the cure of the lymph-node infection.

Total renal deficiency, as differentiated from unilateral renal deficiency, offers explanation of the failure to obtain satisfactory results from antisepsis in some cases through inability to produce a therapeutic concentration of the drug in the efferent channels. This group should include some hypertensive and nephritic cases in which there is fixation of specific gravity of the urine. There is also the danger of storage of these potentially harmful drugs. It is almost unbelievable that in most publications on the use of the mandelic acid and sulfanilamide groups of drugs, there is so free an assumption of the normalness of the kidney function when it is so well recognized that infection in chronic form is one of the commonest causes of renal deficiency.

Renal counterbalance will account for a certain proportion of failures in the treatment of infections. In severe degrees of either acute or chronic infections of one kidney, there is a tendency for the drug to escape so completely through the uninfected functioning kidney that an effective concentration of the drug in the affected kidney is not obtained. Such conditions, if chronic, usually call for surgery.

Special types of bacteria are responsible for the failure of cure in some cases. So wide a variation of results is obtained, and they are so unpredictable, that I am inclined to attempt to clear the infection by use of the sulfanilamide group of drugs. I am willing to accept failure and to try other antiseptics.

There are beginning to appear a few cases of rapid rise in nonprotein nitrogen from the normal reading, which preceded administration of the sulfanilamide group of drugs, to dangerous levels. This rise seems to subside promptly on discontinuance of medication. I have personally noted that in three of four cases of pregnancy injury from combined pre-eclampsia and pyelonephritis, when treated for infection some years after delivery, showed nonprotein nitrogen readings as high as 58 mg. per 100 cc. within three or four days after institution of therapy in doses of 40 to 60 gr. daily.

Recurrences

In a small group of cases, after cure of infection has been produced and confirmed, there is remote recurrence of infection at periods as long as several months or even years. In 19 of 22 such cases, the bacteria were approximately the same as those in the preceding infections. In one case, there was tonsillitis, for which the surgeon justly did not wish to remove the tonsils. In another, there were unrest and chronic exhaustion. One infection was apt to recur at the time of catamenia, and did so on several occasions many months apart. In two cases, there was diverticulosis of the sigmoid. It seems fair to assume that these cases of frequent remote reinfection are the result of failure to discover and to remedy the causal factors of the original infection. The frequency of occurrence of remote infections in the same cases is too great to justify the assumption that they are accidental occurrences.

Special Groups of Infection

There is sufficient evidence of variation from the average in the clinical findings in some cases to warrant giving them special consideration in treatment by urinary antiseptics.

Cases of prostatic obstruction are so frequently deficient in renal function, and retention of nitrogen is so common, that it is not advisable to treat recent postoperative patients for urinary infection without determination of their renal status. It is in this group of patients that I have seen the most serious results from storage of drugs when an attempt has been made to clear their infections before time had been allowed for improvement of renal function after relief of obstruction.

Prostatitis represents a semiclosed infection. It is often associated with urinary-tract infection. Under treatment by antiseptics the urine is more readily cleared of infection than is the prostate. It is recognized that urinary antiseptics may appear in the prostatic secretions, and therefore that the cure of the prostatitis is theoretically possible. Practically, the results of treatment are not good. The possibility of cure in these patients is improved if they are given a period of massage previous to therapy. Since sulfathiazole is quite effective in staphylococcal infections and since many chronic prostatic infections are of that nature, it is to be hoped that this drug will improve results. Marked improvement has been demonstrated in a limited group of cases.

The ureteral and pelvic dilatations of pregnancy create special conditions for harboring urinary-

tract infections. These infections have long baffled therapeutic measures and antisepsis. The use of cystoscopic therapy has had its chief favorable results here and has had wide application. Mandelic acid therapy is not satisfactory in these cases, because acidosis is already marked in the acute stage of the pyelonephritis of pregnancy. Sulfanilamide has proved of particular effectiveness in these cases, to the extent that cystoscopic therapy has seldom been used at the Boston Lying-in Hospital during the last two years. Diagnostic measures, both by intravenous methods and by cystoscopy, have increased. In the majority of these cases, the renal cortex has sufficient function for producing therapeutic concentrations of the drug for antisepsis, in spite of pyelonephritis and large atonic dilatations of the pelvis and ureter. The function is lowest in severe degrees of pyelonephritis. Storage of the drug may be very rapid and of serious consequence if such a condition is bilateral and the patient shows nitrogen retention. One now obtains cure of the infection in approximately 40 per cent of the cases. Traut, Bayer and McLane* claim cures in 55 per cent of their cases.

The routine treatment is to alkalinize the patients and to raise their fluid intake to 3500 or 4500 cc. daily. Sulfanilamide is administered in doses of 40 to 60 gr. daily, without attempting to concentrate the urine, and being careful to maintain alkalization. The treatment is for a period of seven days. Three types of results are produced. In 40 per cent, there is cure of the infection. However, since stasis is the important etiologic factor in the infections of pregnancy, there are a number of cases in which reinfection occurs one or more times during the remainder of the pregnancy. A second group of cases shows diminution and usually cessation of symptoms, but the urine remains cloudy. Another group shows loss of pus, but the infection remains as a bacilluria. It is important to recognize the futility of treating gross pathologic conditions in these cases, except for symptomatic relief. Doses of 60 gr. of sulfanilamide a day are usually preferable to smaller ones. Few cases show improvement if the administration of sulfanilamide is continued beyond a week.

Recent surveys of cases of pyelonephritis of pregnancy indicate that there is almost as much likelihood that mild infections in pregnancy will evidence as much renal damage some years after the injury as severe cases. It is incumbent on those in charge of such patients to treat the women who have bacilluria and mild infections but who may have no symptoms as actively as they do the febrile cases. Sufficient observation should be given to all post-partum cases for three to four months following delivery to determine whether the infection has cleared. In those cases in which there is delayed retrogression of the dilatations of the pelves and ureters, reinfection may occur at any time. If it takes place after demonstration of absence of infection, one may rest in a sense of false security. In some of these apparently cured patients, review of the cases after several years may demonstrate extensive damage to the pelves and ureters, and persistence of the infection.

*Traut, H. F., Bayer, D. S. and McLane, C. M. The prophylaxis of pyelo-ureteritis gravidarum. *J. A. M. A.* 115:94-97, 1940.

Summary

Clinical experience with the more recent additions to the list of urinary antiseptics indicates their increased potency, both for good and harm, over older antiseptics. There is some specificity worthy of the name in these drugs, but it is only relative. There are conditions of renal disease and disordered function in the urinary tract in which cure often cannot be produced by any of the antiseptics. Cure can be accomplished in a considerable number of such cases when, after adequate diagnosis of pathologic and physiologic conditions of the urinary tract, proper remedial measures have been applied or advantage of this information has been taken for better administration of the antiseptic.

99 Commonwealth Avenue

Discussion

Dr. George Gilbert Smith, Boston: With the views expressed by Dr. Crabtree I am in almost complete agreement. He has done well to emphasize two points: the necessity for thorough study of the patient before subjecting him to treatment, and the danger that attends the unwise use of these newer urinary antiseptics. In the early days of sulfanilamide therapy it was reported to be the custom in a hospital remote from here to treat all admissions with sulfanilamide. If they showed no improvement after a few days, a history was taken and a physical examination was made. This may have been a slight exaggeration, but was probably not far from the truth in a good many cases.

The calamities resulting from the unguarded use of sulfanilamide have probably been more numerous than we shall ever know. The chief danger is that of causing agranulocytosis; this may be guarded against by doing a white-cell count at least twice a week. Sudden, fulminating destruction of red blood cells has been reported, but is probably much less frequent than agranulocytosis. The appearance of the patient and determining of the hemoglobin percentage will warn the physician of the development of anemia.

A peculiarity of sulfanilamide that has made its use in a sense disappointing is the temporary nature of the improvement brought about by its administration. This condition exists in gonococcal infections as well as in those of

the upper urinary tract. The sudden clearing of the urine or the disappearance of urethral discharge raises false hopes in the minds of both physician and patient. Experience has taught us to discount this apparent improvement; the drug must be continued for several weeks at least, although the dosage may be decreased to 15 or 20 gr. a day. I have a patient who a year ago was almost incapacitated by recurring attacks of pyelonephritis. He has been taking this amount of sulfanilamide for over a year. To all appearances he is well, but his urine still shows a positive culture for colon bacilli.

It has seemed to me that mandelic acid, if it can be tolerated by the patient, gives more permanent results in removing colon bacilli from the urinary tract than does sulfanilamide. The necessity for concentrating the urine and for keeping it at a pH of 5.3, as Dr. Crabtree has pointed out, makes the administration of mandelic acid somewhat more arduous.

In our enthusiasm for these potent urinary antiseptics we are likely to forget some of the less spectacular but nevertheless useful chemicals. Methenamine, as Dr. Crabtree has said, has cleared up many colon bacillus infections in the past. Serenium has proved very satisfactory in a number of patients, and can be given without fear of complications. With the rapid development of new derivatives of sulfanilamide, we find ourselves somewhat bewildered by the claims of their originators. The wisest course is to stick to the preparation that we have learned to use until others have been definitely proved to be better.

TREATMENT OF MENINGOCOCCAL MENINGITIS*

EDWIN H. PLACE, M.D.†

BOSTON

SINCE Flexner[1] in 1908 first reported his series of cases of meningococcal meningitis treated with antimeningococcus serum, there has been a general acceptance of the influence of serum treatment in this disease. Table 1 gives the comparative results in the earlier years, with a reduction in mortality of nearly 40 per cent in the serum-treated cases.

In the Boston epidemic of 1904–1907 the mortality in 181 cases treated at the Boston City Hospital was 67.3 per cent. In the succeeding eight years the mortality in 50 endemic cases was 58 per cent. The natural course of this form of meningeal infection is much better than that due to infections with other bacteria but has shown great variation, with mortalities ranging from 40 to 90 per cent. In an epidemic in South China Olitsky[3] reported a mortality of 84.6 per cent in 104 cases without treatment and of 54.1 per cent in 346 cases with lumbar puncture only. Cormack[4] recently reported an epidemic in Africa in which, due to lack of serum, only a part of the cases were treated; the mortality in 139 treated cases was 54 per cent, and in 102 untreated it was 82 per cent.

TABLE 1. *Early Results of Serum Treatment.*[2]

AUTHORITY	No. OF CASES	MORTALITY	
		SERUM-TREATED CASES	CONTROL CASES
		%	%
Flexner and Jobling	1300	31	70
Netter	100	28	49
Robb	300	30	72
Dopter	402	16	65
Levy	165	18	52
Steiner	2280	37	77

The reduction in mortality, however, since the introduction of antiserum treatment has been far from satisfactory. In Massachusetts, from 1926 to 1938, in 1474 cases the mortality was 42 per cent, varying in yearly levels from 30 to 66 per cent.[5] In Chicago, from 1916 to 1935, the mortality was 47.7 per cent in 4028 cases (Hoyne[6]); in Detroit, from 1928 to 1931, it was 50.5 per cent in 1686 cases[6]; and in New Orleans, from 1925 to 1934, it was 65 per cent in 221 cases (Tripoli[7]).

The relatively unsatisfactory effects of serum treatment may be due to several causes. In the first place, the serum may not contain an effective level of antibodies for the type of meningococcus causing the infection. The polyvalent serums usually used in this country are produced by the injection into horses of a number of strains, often twelve or more, but the antibody response to each strain may be strikingly different. Furthermore, there is no satisfactory measure of the therapeutic value of antimeningococcus serum except the clinical effect. Wright et al.[8] failed to find that determination of the level of agglutinins was of value in measuring the clinical effectiveness of antiserum. Miller's[9] method of raising the virulence of meningococci with mucin so that they are pathogenic for mice has introduced the possibility of using mouse-protection tests as a measure of potency, but the clinical value of this technic has not been determined. Secondly, the serum may not reach the organisms throughout the subarachnoid space. Meningococci may be walled off in islands of fibrin, and recurrences and relapses occur in about 5 per cent of the cases after apparent clear-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1940.

†Clinical professor of pediatrics, Tufts College Medical School; physician-in-chief, South Department, Boston City Hospital.

ing. The intravenous route has generally been considered unsuited for an antiserum because of the supposed blood-brain barrier (Stern et al.,[10] Mutermilch and Salamon,[11] and Freund[12]). Friedemann et al.[13] have recently shown, however, by ingenious experiments that the blood-brain barrier does not exist for antitoxins, and Hoyne[6] has secured very low mortality rates by intravenous administration alone. Table 2 shows the comparative

TABLE 2. *Comparative Results of Serum Treatment by Different Routes.*

AUTHORITY	NO. OF CASES	MORTALITY
		%
SUBARACHNOID		
Flexner and Jobling[1]	393	25
Bolduan[14]	143	26
Appelbaum[15]	302	18
Smith, Maxson and Murphey[16]	56	41
Total	894	24
INTRAVENOUS AND SUBARACHNOID		
Hoyne[6]	201	27
Banks[17]	38	16
Smith, Maxson and Murphey[16]	75	36
Bolduan[14]	48	21
Tillett and Brown[18]	19	5
Total	381	26
INTRAVENOUS		
Hoyne[6]	96	16

results of serum treatment by different routes. Hoyne, in 43 cases under twenty years of age treated intravenously, reported a record mortality of 2.3 per cent.

There is great difficulty in evaluating results because of variation in virulence and type of the organisms, the use of different amounts of serum of varying antibody titers and the difference in the patients' ages and in the time of treatment. The

TABLE 3. *Effect of Time of Treatment, According to Age.*

AGE	MORTALITY		
	TREATED BEFORE 4TH DAY	TREATED 4TH TO 7TH DAY	TREATED 7TH DAY OR LATER
yr.	%	%	%
Less than 2	0	20	58
2–5	12	30	24
5–10	9	16	17
10–20	12	23	37
20 or over	30	32	28

mortality below one year of age and above forty years is very high, and that above fifty years approximates 100 per cent. Flexner[1] showed the importance of early treatment, which was especially marked during infancy (Table 3).

The value of Ferry's[19] antitoxin as compared to antiserum still remains uncertain. In 1936 Hoyne[6] reported 201 antitoxin-treated cases, with a mortality of 27 per cent. He gives large doses intravenously —50,000 to 100,000 units (150 to 300 cc.). Banks[20] had a mortality of 28 per cent in 25 cases treated with antitoxin. A number of reports of antitoxin treatment of meningitis, usually of small numbers of patients, have shown good results, but due either to lack of controls or to obvious differences in age or time of treatment in the groups the figures are not dependable. Ferry's antitoxin contains antibacterial antibodies, and Zinsser[21] believed that "the therapeutic activity of so-called meningococcus antitoxin is due to the presence of antibacterial and antiendotoxic antibodies."

For intraspinous use, the dose naturally is limited, and variation of dosage must be secured by injection at different intervals. Bolduan[14] at Bellevue Hospital showed much better results with twelve-hour (7 per cent mortality) than with twenty-four-hour (23 per cent mortality) intervals.

TABLE 4. *Effect of Sulfanilamide Therapy.*

AUTHORITY	NO. OF CASES	MORTALITY
		%
Waghelstein[22]	72	15
Carey[23]	5	0
Banks[20]	16	6
Eldahl[24]	12	25
Willien[25]	5	0
Jewesbury[26]	6	0
Muraz, Chirle and Quéguiner[27]	271	11
Place[28]	25	12
Total	412	11

In the recent Boston epidemic the mortality was 48 per cent, with eight-hour to twelve-hour intervals.

Some workers believe that overtreatment may do harm. In judging the discontinuance of serum therapy, a drop in the number of cells and in the amount of cerebrospinal fluid, disappearance of the organism in culture and clinical improvement must all be considered. Since serum reactions may keep up the pleocytosis and an increase in the amount of cerebrospinal fluid, the chief dependence must be on smears and cultures.

During the last three years, sulfanilamide has been used with a generally lower mortality than that secured with serum (Table 4).

Branham and Rosenthal[29] have shown experi-

TABLE 5. *Effect of Combined Serum and Sulfanilamide Therapy.*

AUTHORITY	NO. OF CASES	MORTALITY
		%
Banks[17]	59	12
Smith, Maxson and Murphey[16]	16	13
Muraz, Chirle and Quéguiner[27]	23	9
Total	98	11

mentally in mice that serum and sulfanilamide together were more effective than sulfanilamide alone in four of ten strains. Similar results were obtained by Brown.[30] Clinically no clear evidence has been secured that serum is usually necessary

when sulfanilamide is used. But since occasional cases may not respond to the drug treatment, it may be desirable to use serum, although probably only small amounts will be needed. Table 5 shows the results of combined serum and sulfanilamide therapy; the average mortality rate is the same as that for sulfanilamide alone.

One of the most striking effects of sulfanilamide treatment is the rapid subsidence of symptoms and the spinal-fluid pleocytosis, and the rapid disappearance of the organisms from the blood and spinal fluid, usually in twenty-four hours. Blackfan[2] found in 33 cases treated with antimeningococcus serum that organisms could be recovered after the third day in 51 per cent, and Levy[31] in 144 cases recovered meningococci after the third day in 24 per cent. In the 25 cases treated by us with sulfanilamide no organisms could be recovered after the third day, except in one case.

Relapses after serum treatment were reported by Flexner[1] in 4.5 per cent of 427 cases, and Worster-Drought and Kennedy[32] reported relapses in 5 per cent. Tillett and Brown[18] in the Baltimore epidemic, in which they used a very effective serum, still had recrudescences or relapses in 11.5 per cent. Relapses and recurrences after sulfanilamide have been reported in only 0.5 per cent,[20, 22–28] and these have occurred without exception with inadequate treatment. The drug should promptly reach a level in the spinal fluid of 5 to 10 mg. per 100 cc., although lower concentrations are often effective.

Oral administration is entirely satisfactory; if vomiting is present, the drug may be given subcutaneously in 0.8 per cent solution or intrathecally.

Untoward effects of the drug must be continually watched for. These are too well known to require review. In our series they were rarely significant. The use of sulfanilamide alone has given an opportunity to judge the harmful effects of intrathecal serum, as distinguished from local effects of the disease itself. Although our experience has been too small for satisfactory analysis, we were struck by the decrease in spinal-fluid block and in myelitic and cerebral damage and by the absence of pressure abnormalities in the sulfanilamide-treated cases. The same effect has been noted by Hoyne[6] following intravenous serum therapy as contrasted with intrathecal treatment.

Meningococcemia has disappeared promptly following sulfanilamide treatment, even in cases found resistant to serum therapy.

Meningococcal arthritis usually tends to subside, even without efficient therapy. Tillett and Brown[18] found arthritis in 43 per cent of their cases. All cleared, though some slowly, with intravenous and intrathecal therapy. Sufficient evidence of control of arthritis by chemotherapy is still lacking, but our cases have shown rapid subsidence. Schein[33] in a recent report of 23 cases of meningococcal arthritis discredits somewhat the optimistic prognostic view so generally held. Several of his cases had persistent trouble and in 3, or 13 per cent, there was permanent joint damage, with destruction and ankylosis. In 2 cases of severe purulent meningococcal arthritis we have followed the technic, so successfully used in streptococcal arthritis, of mechanically washing out the joint, with prompt and complete recovery.

The dosage of sulfanilamide recommended by Long and Bliss[34] seems adequate:

Weight of Patient	Initial Dose	Subsequent 4-Hr. Dose
lb.	*gr.*	*gr.*
100 or more	50–80	15
50–90	30–50	10–15
25–50	20–30	5–10

The advantages of sulfanilamide are that administration is simple; it is independent (largely) of type of organism; the dosage can be reasonably accurate, and the concentration is measurable; inadequacy of original titer or loss from keeping, as in serum, is excluded; the drug is much cheaper; the mortality is lower; there is apparently less neurologic damage.

745 Massachusetts Avenue

References

1. Flexner, S. and Jobling, J. W. Serum treatment of epidemic cerebro-spinal meningitis. *J. Exper. Med.* **10**:141-203, 1908. An analysis of four hundred cases of epidemic meningitis treated with the antimeningitis serum. *Ibid.* **10**:690-733, 1908.
2. Blackfan, K. D. Treatment of meningococcus meningitis. *Medicine* **1**:139-212, 1922.
3. Olitsky, P. K. Experiences with a recent epidemic of meningococcic meningitis among a Chinese civil population. *Arch. Int. Med.* **23**:380-394, 1919.
4. Cormack, R. P. On value of serum-treatment of cerebro-spinal fever. *East African M. J.* **12**:311, 1936.
5. *Annual Reports* (1926–1938). Department of Public Health, Commonwealth of Massachusetts.
6. Hoyne, A. L. Intravenous treatment of meningococcic meningitis with meningococcus antitoxin. *J. A. M. A.* **107**:478-481, 1936.
7. Tripoli, C. J. Bacterial meningitis: comparative study of various therapeutic measures. *J. A. M. A.* **106**:171-177, 1936.
8. Wright, I. S., De Sanctis, A. G. and Sheplar, A. E. Determination of value of serum in treatment for meningococcus meningitis: report of illustrative series of cases. *Am. J. Dis. Child.* **38**:730-740, 1929.
9. Miller, C. P. Study of experimental meningococcal infection. *Proc. Soc. Exper. Biol. & Med.* **32**:1136-1142, 1935.
10. Stern, L., Kassel, G. N., Lokschina, E. S., Romel, E. L. and Zeitlin, S. M. A propos du passage des anticorps du sang dans le liquide céphalorachidien. *Compt. rend. Soc. de biol.* **99**:360-362, 1928.
11. Mutermilch, S. and Salamon, E. Sur l'immunité méningée passive et active. *Compt. rend. Soc. de biol.* **108**:696-699, 1931.
12. Freund, J. Accumulation of antibodies in central nervous system. *J. Exper. Med.* **51**:889-902, 1930.
13. Friedemann, U., Zuger, B. and Hollander, A. Quantitative studies on neutralization of pathogenic agents in tissues (circulating antibodies: permeability of cerebral capillaries to antibodies). *J. Immunol.* **36**:219-230, 1939.
14. Bolduan, N. W. Treatment of meningococcus meningitis: intraspinal use of antimeningococcus serum at Bellevue Hospital, 1928 to 1936. *J. Pediat.* **13**:357-363, 1938.
15. Appelbaum, E. Immunological aspects and treatment of meningitis. *Arch. Pediat.* **55**:400-416, 1938.
16. Smith, T. C., Maxson, W. T. and Murphey, D. F. H. Meningococcus meningitis: observations in one hundred and fifty-seven cases in Louisville City Hospital. *South. M. J.* **31**:1168-1171, 1938.
17. Banks, H. S. Serum and sulphanilamide in acute meningococcal meningitis: preliminary survey based on one hundred and thirteen cases. *Lancet* **2**:7-13, 1938.
18. Tillett, W. S. and Brown, T. McP. Epidemic meningococcus meningitis: an analysis of twenty-six cases, twenty-one of which occurred in the spring of 1935. *Bull. Johns Hopkins Hosp.* **57**:297-316, 1935.

19. Ferry, N. S. Meningococcus antitoxin: prophylactic and therapeutic tests on guinea pigs. *J. Immunol.* 23:315-324, 1932. Meningococcus toxin and antitoxin: further tests on monkeys. *Ibid.* 26:133-141, 1934.
20. Banks, H. S. Note on Ferry's meningococcus antitoxin in treatment of acute cerebro-spinal fever. *Lancet* 1:856-858, 1935.
21. Zinsser, H., Enders, J. F. and Fothergill, L. D. *Immunity: Principles and application in medicine and public health.* Fifth edition of *Resistance to Infectious Diseases.* 801 pp. New York: Macmillan Co., 1939.
22. Waghelstein, J. M. Sulfanilamide in treatment of 106 patients with meningococcic infections. *J. A. M. A.* 111:2172-2174, 1938.
23. Carey, B. W., Jr. Use of para-aminobenzenesulfonamide and its derivatives in treatment of infections due to *B* Streptococcus hemolyticus, meningococcus, and gonococcus: report of thirty-eight cases. *J. Pediat.* 11:202-211, 1937.
24. Eldahl, A. Intrathecal sulphanilamide in meningococcal meningitis. *Lancet* 1:712-715, 1938.
25. Willien, L. J. Sulfanilamide therapy in meningococcic meningitis. *J. A. M. A.* 110:630-632, 1938.
26. Jewesbury, E. C. O. Use of sulphanilamide in treatment of meningococcal meningitis. *Lancet* 1:1262-1264, 1938.
27. Muraz, G., Chirle, H. and Quéguiner, A. Essais comparés de traitements (sérum; corps azoïque; sulfanilamide) de la méningite cérébro-spinale dans des régions coloniales rurales (Niger français). *Presse méd.* 46:1113-1116, 1938.
28. Place, E. H. Sulfanilamide in meningococcic infections. *M. Clin. North America* 23:1159-1172, 1939.
29. Branham, S. E. and Rosenthal, S. M. Studies in chemotherapy: sulphanilamide, serum, and combined drug and serum therapy in experimental meningococcus and pneumococcus infections in mice. *Pub. Health Rep.* 52:685-695, 1937.
30. Brown, T. M. Protective action of sulfanilamide and antimeningococcus serum on meningococcus infection of mice. *Bull. Johns Hopkins Hosp.* 61:272-279, 1937.
31. Levy: cited by Blackfan.[2]
32. Worster-Drought, C. and Kennedy, A. M. Cerebro-spinal fever: the mode of invasion by the meningococcus. *Lancet* 2:711-714, 1917.
33. Schein, A. J. Articular manifestations of meningococcic infections. *Arch. Int. Med.* 62:963-978, 1938.
34. Long, P. H. and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds.* 319 pp. New York: The Macmillan Co., 1939.

SKIN MANIFESTATIONS DUE TO SULFANILAMIDE AND ITS DERIVATIVES*

ARTHUR M. GREENWOOD, M.D.†

BOSTON

IT is possible roughly to classify the effects on the skin of the therapeutic use of sulfanilamide and its derivatives under the three categories suggested by Loewy[1] in a discussion of the effects of prolonged administration of drugs. These are the direct toxic effects due to overdose and cumulation, the purely allergic effects, producing manifestations identical with those seen in consequence of antigen-antibody reactions in protein anaphylaxis, and the allergotoxic effects. In the last category an overdose can usually be excluded and a peculiar sensitivity due to gradual sensitization is evident. The manifestations are different from the purely allergic, anaphylactic reactions, and are fairly characteristic for the cumulative drug, which probably acts indirectly on the protein metabolism. Such an allergotoxic effect is responsible for most drug idiosyncrasies.

The accuracy of such a classification is debatable, and in the use of sulfanilamide particularly, the accompanying rashes are so multiform that hard and fast categories cannot be adhered to, so far as objective appearance of the eruption is concerned. There is no single rash characteristic of sulfanilamide and its derivatives.

Without seeming to be too definite, one may say that in many cases the first manifestations of the toxic type of eruption are shown by a faint, finely papular rash on the arms — perhaps accompanied by mild itching and fever. If the drug is continued, the rash spreads and becomes maculopapular, scarlatiniform or morbilliform. It may involve the whole body or may be limited to various parts. There is no lymphadenitis accompanying it. On cessation of the drug, the fever goes and with it the rash, occasionally leaving the involved surfaces desquamating — at other times leaving no trace. In certain cases the rash disappears even though the drug is continued. In others, after cessation of sulfanilamide and the disappearance of the rash, the drug may be resumed in moderate dosage without untoward symptoms. Such cases may be considered to be due to direct toxicity of the drug, either from primary overdosage for the patient or from accumulation. There is no allergy and no gradually built-up sensitization.

Cases illustrative of the second type, the purely allergic effect, show early in the course of administration of sulfanilamide intense itching, sneezing, lachrymation and dyspnea, with edema of the lips, eyelids and face. The eruption may be urticarial, hemorrhagic or bullous. Patch and scratch tests may be positive for the drug.

Cases showing the allergotoxic effect, that of gradual sensitization, ordinarily appear later in the course of therapy — from the seventh to the fourteenth day of average dosage of sulfanilamide. The eruption is generally maculopapular and accompanied with pruritus and urticarial lesions, with fever and, in some cases, leukocytosis. Resumption of sulfanilamide, after cessation and the disappearance of the rash, is quite certain to bring on a recurrence of the reaction.

All reports and observation show the multiform character of sulfanilamide rashes. They may be erythematous, papular, morbilliform, scarlatiniform, urticarial, petechial or bullous; the mucous membranes may be affected; the rash may be limited or general, accompanied or unaccompanied by fever and itching. Exfoliative dermatitis has been a sequel in some cases. One case has been

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1940.

†Dermatologist, New England Deaconess Hospital.

reported in which a fixed eruption was produced by sulfanilamide and sulfapyridine.[2] Most cases, however, are maculopapular, not generalized, and are accompanied by fever and pruritus. Although there is no specific characteristic for the rash, numerous reports and my own observations stress its peculiar, almost maroon color in many cases, and this very intensity of the superficial vascular reaction in a fully developed case constitutes an identifying factor.

In spite of this lack of specificity of the lesions, it is not difficult to make the correct diagnosis of the eruption appearing in the course of treatment, and the only difficulty is to distinguish the morbilliform type from measles and the scarlatiniform type from scarlet fever. It has been noted that the average interval between beginning administration of the drug and the appearance of the rash falls within the period of incubation of the common infectious fevers.[3] With a morbilliform sulfanilamide rash, however, Koplik's spots, catarrhal symptoms and lymphadenitis are not present, and in a scarlatiniform rash the characteristic tongue and throat of scarlet fever are absent.

There is some evidence to show that persons sensitive to local anesthetics and those who have had other drug rashes are likelier to be sensitive to sulfanilamide.

The eruption is likely to occur in from 2 to 6 per cent of cases treated with average dosage, with a higher incidence, 30 per cent, in cases intensively treated.[4] It has been shown that sulfanilamide in certain concentration and in certain persons is a photosensitizing agent and that in such patients the rash is confined to exposed surfaces, or is more intense over such areas.[5, 6] Although not all cases of sulfanilamide eruption can be considered to be dependent on exposure to sunlight, it is definitely advisable that all patients under sulfanilamide therapy be protected from direct sunlight or ultraviolet radiation.

It has been found that in certain cases of sulfanilamide dermatitis there is an increase in urinary porphyrins.[7, 8] Such increases, however, may occur in association with various disorders accompanied by severe derangement of the general metabolism, and increased values are not found in all cases of sulfanilamide dermatitis. Long and Bliss[9] state that in their opinion the role played by the production of porphyrins in sulfanilamide dermatitis has not been investigated sufficiently to warrant a final word on the subject. Brunsting[8] says that whereas light sensitization and porphyria may appear at the same time there is no evidence to show that one condition is dependent on the other.

In the use of sulfathiazole apparently a somewhat higher incidence of skin reactions is to be expected. Haviland and Long[10] report 12.8 per cent of eruption and state that the rashes fall in three groups — maculopapular, urticarial and those like erythema nodosum. This last group has not been reported in connection with sulfanilamide or sulfapyridine medication. They also report a new type of reaction with this drug — a conjunctival and scleral injection restricted mainly to the exposed portion of the bulbar conjunctiva and sclera, and in some cases apparently dependent on exposure to light. I have seen one such case, in which there was pronounced congestion and edema of the ocular and palpebral parts of the conjunctiva occurring on the ninth day of sulfathiazole medication, in a patient confined to the ward and in whom a very slight rash appeared. Of 13 cases treated at the Massachusetts General Hospital with sulfathiazole in moderate dosage, 6 showed a rash — a much higher incidence than has previously been reported.

Summary

It can be said that the rashes occurring in the course of therapy with sulfanilamide or its derivatives are multiform in character and are not specific, with the possible exception of those following the use of sulfathiazole; that they may be manifestations of toxemia, sensitization or allergy; that they may occur at any time in the course of treatment, but generally from the fourth to the fourteenth day, and in from 2 to 30 per cent of the cases, depending on the intensity of treatment. They are likelier to appear in areas exposed to sunlight and may be accompanied by an increase in the excretion of porphyrins. The occurrence of a rash is a warning of danger, and treatment with sulfanilamide or its derivatives should be stopped and not renewed unless the gravity of the case warrants it; if treatment is to be resumed the patient should be tested for sensitivity with small (0.3 gr.) doses of the drug.

416 Marlboro Street

References

1. Loewy, F. E. Thrombopenic haemorrhagic purpura due to idiosyncrasy towards the hypnotic Sedormid. *Lancet* **1**:845, 1934.
2. Loveman, A. B. and Simon, F. A. Fixed eruption and stomatitis due to sulfanilamide. *Arch. Dermat. & Syph.* **40**:29-34, 1939.
3. Thompson, A. R. M & B 693 rashes, with particular reference to acute exanthemata. *Brit. M. J.* **2**:13, 1939.
4. Townsend, T. M. and Mulcahy, T. M. Sulfanilamide in treatment of urological infections. *New York State J. Med.* **38**:833-835, 1938.
5. Newman, B. A. and Sharlit, H. Sulfanilamide: photosensitizing agent of skin. *J. A. M. A.* **109**:1036, 1937.
6. Brunsting, L. A. Sulfanilamide dermatitis: question of relation to photosensitivity. *Proc. Staff Meet., Mayo Clin.* **12**:614-616, 1937.
7. Rimington, C. and Hemmings, A. W. Porphyrinuria following sulphanilamide: sulphanilamide dermatitis. *Lancet* **1**:770-776, 1938.
8. Brunsting, L. A., Brugsch, J. T. and O'Leary, P. A. Quantitative investigation of porphyrin metabolism in diseases of the skin. *Arch. Dermat. & Syph.* **39**:294-307, 1939.
9. Long, P. H. and Bliss, E. A. *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds.* 319 pp. New York: The Macmillan Co., 1939.
10. Haviland, J. W. and Long, P. H. Skin conjunctival and scleral reactions in the course of therapy with sulfathiazole. *Bull. Johns Hopkins Hosp.* **66**:313-318, 1940.

CRIMINAL ASPECTS OF FAITH HEALING

I. H. RUBENSTEIN*

CHICAGO

THE question that this article seeks to answer is, What are the criminal aspects of faith healing and its practice, particularly when infant children die as a result of lack of medical care that their parents refuse to provide because of their religious convictions as members of a faith-healing cult? To understand the several criminal aspects of this question, it is necessary to know what faith healing means. Faith healing is simply the treatment of human ailments, injuries and diseases by mental and spiritual means, that is, by mental "reasoning," argument and prayer. Because of the strong emotional appeal that faith healing has for the public in general, this age-old doctrine has been exploited by numerous "founders and discoverers" of faith-healing sects, especially in the last hundred years.

The first point to consider in this article, therefore, is how the courts have viewed the subject of faith healing itself. In a Pennsylvania case,[1] the court stated:

> Common faith of mankind relies not only upon prayer, but [also medical care]. . . . Our laws recognize disease as a grim reality to be met and grappled with as such. . . . It may be said that the wisdom or folly of depending upon the power of inaudible prayer alone, in the cure of disease, is for the parties who invoke such a remedy. But this is not wholly true. "For none of us liveth to himself, and no man dieth to himself," and the consequence of leaving disease to run unchecked in the community is so serious that sound public policy forbids it. Neither the law, nor reason, has any objection to the offering of prayer for the recovery of the sick. But in many cases both law and common sense require the use of other means [medical care] which have been given to us for the healing of sickness and the cure of disease. There is ample room for the office of prayer, in seeking for the blessing of restored health, even when we have faithfully and conscientiously used all the means known to science and the art of medicine.

As clearly indicated by the reasoning of the court in this case, faith healing constitutes a grave menace and danger to the public health, when used as a substitute for medical care, especially when infectious and contagious diseases are involved. For this reason, as well as others, the courts have viewed with strong disfavor,[2] and have even condemned,[1, 3] any institution that encourages the growth and spread of faith healing. At present, the law is well established that as a matter of public policy the proper public authorities may restrict and even prohibit the practice of faith healing if it should in any way endanger the public health.[4]

Having given sufficient consideration to the subject of faith healing itself, the next point to consider is whether the practice of faith healing constitutes a violation of the several medical-practice acts. Although practically all the medical-practice acts expressly exempt "those persons who endeavor to heal or cure the sick and suffering by prayer or spiritual means or as an exercise of the tenets of their religion" from their penal provisions, a large number of faith healers of various cults have been convicted in many states on criminal charges for violation of these acts.[5] In those cases in which the courts have held that faith healers do come within this statutory exemption, the treatment is exclusively spiritual and religious,[6] — that is, confined solely to prayer,[7] —and is not accompanied by the use of any physical means whatever. A faith healer would therefore be subject to the penal provisions of any of the several medical-practice acts if he also made use of any of the following physical agencies or means: giving a diagnosis of the patient's ailment, injury or disease,[8] giving treatment based on such a diagnosis,[9] asking pertinent questions of the patient as to his ailment, giving massage,[10] recommending or giving any herbs, liquids,[11] chemical preparations,[12] or physical exercises, using any physical instrument, giving directions as to food or diet,[13] or directly advising the patient to discontinue or abstain from medical or surgical treatment.[3,4] Faith healers may also be prohibited from giving treatments that might endanger the public health,[4] especially if they are violative of statutory quarantine and sanitary regulations. Even in those cases in which the faith healer confines his treatments exclusively to spiritual means, he may be subject as an offender of the medical-practice act when it is shown that he is exploiting faith healing for commercial profit. As was well stated by a Colorado court[14]:

> One is not authorized . . . under the cover of religion or a religious exercise . . . to go into healing commercially for hire, using prayer as the curative agency or treatment. Religion cannot be used as a

*Member of the Chicago Bar.

> shield to cover a business undertaking.* . . . The practice of medicine, defined by our statute, means the practice of the healing art commercially, regardless of the curative agency employed.† The commercial practice of healing by prayer, followed as a money-making venture or occupation, is the practice of medicine within the plain meaning of the statute.[15]

This ruling is particularly applicable when the faith healer gives treatments to his patients in an office building, apart from his own home or the home of the patient, or in the church edifice, and there charges compensation for his treatments.[16]

When a faith healer is prosecuted for a criminal violation of the medical-practice act, the issue of constitutional religious freedom is always raised. On this point, however, the law is well settled: although the government may not interfere with mere religious belief and opinions, it can prohibit and punish religious practices that are criminal offenses.‡ Since the violation of a state medical-practice act is a criminal offense, it can readily be seen that a faith healer whose practices make him guilty of such an offense[5] may not claim the defense of constitutional religious freedom.[19]

The next and most important point for consideration is the criminal responsibility of parents who allow their infant children to die as a result of their refusal to provide them with the necessary medical care, because of a conscientious belief in faith healing. Under the law, medicines and medical attention furnished an infant, when his health or physical condition requires them, are necessities because they answer the bodily needs of the infant.[20]§ By the law of Nature, as well as the common law, and independently of statute, it may be generally stated that parents are under an obligation to care for their young in sickness and in health, and to do whatever may be required for their care and maintenance, including medical attendance if necessary. The failure to provide such medical care is a public wrong, and if the infant child is injured, the parent can be convicted of the criminal neglect of his child¶; should the child die as a result of such neglect, the parent would be guilty of manslaughter.[23] The law is the same in such cases, even though the neglect of the parents was due entirely to their superstitious or conscientious opinions that it is wrong and irreligious to provide medical aid for their children or themselves.[24] In other words, the law may be stated to be that a parent, guardian, relative or any other person, who has the custody of a person "who is unable, by reason of . . . age . . . to withdraw himself from such charge, [is under a duty] to supply that person with the necessaries of life, medical attention . . . included, and that where one by reason of his religious belief fails to provide medical treatment for a child, he may in case of the death of the child, be convicted of manslaughter."[25]‖

In the leading English case,[26] the defendant was the father of an eight-month-old infant. The child died of diarrhea and pneumonia. The prisoner had not supplied his child with any medical care, because he was a member of a sect, called the "Peculiar People," which believed in faith healing and disbelieved in the necessity of physicians and medicines. The medical testimony was that medical assistance would certainly have prolonged and in all probability would have saved the child's life. The prisoner was indicted under a Prevention of Cruelty to Children Act, which read: "If any person . . . who has the custody, charge or care of any child . . . wilfully . . . neglects . . . such child . . . in a manner likely to cause such child . . . injury to health, that person shall be guilty of a misdemeanor." The prisoner was convicted of manslaughter. In affirming the manslaughter conviction, the eminent Chief Justice Lord Russell declared:

> The [meaning of the] words in the statute, "wilfully neglects" . . . is very clear. "Wilfully" means that the act is done deliberately and intentionally, not by accident or inadvertence, but so that the mind of the person who does the act goes with it. "Neglect" is the want of reasonable care, that is, the omission of such steps as a reasonable parent would take, such as are

*A school for training faith healers was held irreligious because founded solely for the pecuniary benefit of its founders and officers.[3]

†The giving of treatment by a faith healer for a fee constitutes the practice of medicine and makes the faith healer subject to criminal prosecution.[15]

‡The First Amendment to the Constitution of the United States declares that "Congress shall make no law respecting an establishment of religion or prohibiting the free exercise thereof." This amendment, which guarantees religious liberty and which exists in similar paraphrased form in all the state constitutions, has been interpreted to mean "to allow everyone under the jurisdiction of the United States to entertain such notions respecting his relations to his Maker and the duties they impose as may be approved by his judgment and conscience, and to exhibit his sentiments in such form of worship as he may think proper, not injurious to the equal rights of others, and to prohibit legislation for the support of any religious tenets, or the modes of worship of any sect. . . . It was never intended or supposed that the Amendment could be invoked as a protection against legislation for the punishment of acts inimical to the peace, good order and morals of society. . . . However free the exercise of religion may be, it must be subordinate to the criminal laws of the country, passed with reference to actions regarded by general consent as properly the subjects of punitive legislation. . . . Should a sect [with tenets encouraging crime] ever find its way into this country, swift punishment would follow the carrying into effect of its doctrines, and no heed would be given to the pretence that, as religious belief, their supporters could be protected in the exercise by the Constitution of the United States." [17] "To permit a man to excuse his criminal practices because of his religious belief . . . would be to make the professed doctrines of religious belief superior to the law of land, and in effect permit every citizen to become a law unto himself. Government could exist only in name under such circumstances." [18] Therefore no plea of religion can shield a person who commits a criminal offense, because the public would be at the mercy of superstition, if criminal offenses could be "committed with impunity, because sanctioned by some religious delusion." [19]

§"It is undisputed that medicine as a science, is now and has been for a long period of time, generally recognized by the law, and the efficacy of medical treatment by a skilled and competent physician is universally conceded." [21]

¶A father, who refused to allow his infant child to be operated on for adenoids, which were impairing the child's health, was held to be liable for criminally neglecting to provide his child with medical care.[22]

‖To sustain a manslaughter conviction in these cases, it is necessary for the medical testimony to show that the neglect to obtain medical care *hastened* or *caused* the death of the child, and not merely that the medical care would have prolonged the life of the child.

> usually taken in the ordinary experience of mankind, that is, in such a case as the present. . . . At the present day, when medical aid is within the reach of the humblest and poorest members of the community, it cannot reasonably be suggested that the omission to provide medical aid for a dying child does not amount to neglect. Mr. Sutton [counsel for the prisoner] contended that because the prisoner was proved to be an affectionate parent, and was willing to do all things for the benefit of his child except the one thing which was necessary in the present case, he ought not to be found guilty of the offense of manslaughter, on the ground that he abstained from providing medical aid for his child in consequence of his peculiar views in the matter; but we cannot shut our eyes to the danger which might arise if we were to accede to that argument, for where is the line to be drawn? In the present case, the prisoner is shewn to have had an objection to the use of medicine; but other cases might arise, such, for instance, as the case of a child with a broken thigh, where a surgical operation was necessary, which had to be performed with the aid of an anesthetic. Could the father refuse to allow the anesthetic to be administered? Or take the case of a child that was in danger of suffocation, so that the operation of tracheotomy was necessary in order to save its life, and an anesthetic was required to be adminstered. I am of the opinion . . . the conviction ought to be affirmed.

Likewise in accord with the preceding authoritative English case is the leading Canadian case.[27] Here, the defendant was a Christian Scientist. He was the father of a six-year-old boy. The child was ill with diphtheria and subsequently died of the disease. During the time that the boy was ill, he was given Christian Science treatments by a Christian Science "demonstrator." The prisoner, a man of financial means, admitted that if he had not been a Christian Scientist, he would have called in a physician. He was indicted under the criminal code for failing to supply necessities for his child, that is, to provide medical care, and he was convicted of manslaughter. In affirming the conviction, the Ontario Court of Appeals declared:

> No matter how earnestly a parent might believe in the efficacy of Christian Science treatment, as developed in Mrs. Eddy's handbook of the doctrines of the sect, yet if they came to the conclusion that medical aid and treatment was necessary, they ought also to find that it would not be furnished by means of mental treatment by a Christian Science "demonstrator." Persons sui juris may by mutual consent, and within certain limits, practice upon each other what experiments of this kind they please. . . . But it would be shocking if in the case of infants or others incapable of protecting themselves, they and the community in which they live were to be exposed to the danger from contagious or infectious diseases which the instructed common sense of mankind in general does not as yet find or admit to be curable by means only of subjective or mental treatment.

Also in accord with the reasoning of the English and Canadian authorities are the American courts. In the leading American case,[28] the defendant had a sixteen-month-old daughter, who contracted whooping cough, which afflicted her for thirty days, when catarrhal pneumonia developed and caused her death three days later. The defendant testified that forty-eight hours before the child died, he observed that her symptoms were of a dangerous character, but that he did not send for or call a physician to treat her, although he was financially able to do so. His reasons for not doing so were that he was a member of a faith-healing sect, known as the Christian Catholic Church, the teachings of which denied the need of medical aid, and that his religion led him to believe that the child would get well by prayer. The defendant was indicted and convicted of a misdemeanor. In affirming the conviction, the Court of Appeals of New York declared:

> The peace and safety of the state involves the protection of the lives and health of its children as well as the obedience to its laws. . . . Children when borne into the world are utterly helpless, having neither the power to care for, protect or maintain themselves. They are exposed to all the ills to which the flesh is heir, and require careful nursing, and at all times, when danger is present, the help of an experienced physician. . . . A person . . . cannot, under the belief or profession of [religious] belief that he should be relieved from the care of children, be excused from punishment for slaying those who have been borne to him.

Although the father was convicted only of a misdemeanor, one commentator[29] stated that it does not appear why the father "was not indicted for manslaughter, since his child died as a result of his failure to provide medical aid."

In two Pennsylvania cases,[30, 31] in which the facts were similar to the Pierson case, the conviction of the father on manslaughter charges was affirmed. In its reasoning for its decision, one Pennsylvania court[30] declared:

> If the case of sickness be such that ordinary prudence would suggest the services of a physician and the use of proper medicines, then such services and medicines would be necessaries in that case, and failure to employ the one and use the other, if reasonably within reach, would be negligence on the part of the person on whom the duty rested, and if by reason of such neglect, on the part of the father, the death of a child ensues, he would be guilty of manslaughter.

In the other case,[31] the court stated that the father cannot relieve himself of his legal duty to provide medical care to his child,

> because of some religious or conscientious belief. In no instance is this more true than in the case of a helpless infant unable to take any action for its own assistance or relief and incapable of exercising judgment as to what should be done. . . . If persons were permitted

> to plead, as giving them immunity from acting contrary to enactments of law, their religious belief, . . . the whole policy of the state relative to health laws would be defeated.

Because such neglect on the part of a parent to provide the necessary medical care to his infant child is pursuant to a religious belief, and is a religious practice, which nonetheless is a criminal offense,[25] the defense of constitutional religious freedom is of no avail in such cases.[17–19] If the infant child dies, the faith healer can be convicted as an accomplice, as an accessory before the fact,[32] or even as a principal, on manslaughter charges, if the evidence shows that, in addition to prayer, he made use of any physical means or agency.*

*In two cases,[33] faith healers were acquitted because they confined their treatments exclusively and solely to prayer.

205 West Wacker Drive

References

1. First Church of Christ, Scientist, 205 *Penn. St.* 543, 55 *Atl.* 536 (1903).
2. Lange v. Hoyt, 114 *Conn.* 590, 159 *Atl.* 575 (1932).
3. In re St. Louis Institute of Christian Science, 27 *Mo. App.* 633 (1887).
4. State ex rel. Stone v. Probst, 165 *Minn.* 361, 206 *N. W.* 642 (1925).
5. *Christian Science practitioners:* State v. Marble, 72 *Ohio St.* 21, 73 *N. E.* 1063 (1905); State v. Buswell, 40 *Neb.* 158, 58 *N. W.* 728 (1894); Kansas City v. Baird, 92 *Mo. App.* 204 (1902). *Spiritualist healers:* People v. Krause, 291 *Ill.* 64 (1920); People v. Vogelgesang, 221 *N. Y.* 290, 116 *N. E.* 977 (1917). *Faith healers:* Smith v. People, 51 *Col.* 270 (1911); People v. Moser, 176 *Ill. App.* 625 (1913); People v. Jones, 92 *Ill. App.* 447 (1900); People v. McTier, 184 *Ill. App.* 635 (1914); Rex v. Brooks, 9 *Brit. Col.* 13 (1902); State v. Peters, 87 *Kan.* 265, 123 *Pac.* 751 (1912); State v. Pratt, 92 *Wash.* 200, 158 *Pac.* 981 (1916). *Magnetic healers:* People v. Gordon, 194 *Ill.* 560 (1902); People v. Trenner, 144 *Ill. App.* 275 (1908); Parks v. State, 159 *Ind.* 211 (1902). *Yogi healer:* Singh v. State, 66 *Tex. Cr. R.* 156 (1912). *Christian Philosopher healer:* People v. Cosper, 76 *Cal. App.* 597, 245 *Pac.* 466 (1926). *Altrurian Society healer:* Fealy v. City of Birmingham, 15 *Ala. App.* 367, 73 *So.* 296 (1916).
6. People v. Jones, 92 *Ill. App.* 447 (1900). State v. Mylod, 20 *R. I.* 632, 40 *Atl.* 753 (1898). Evans v. State, 9 *O. D.* 222 (1889).
7. People v. Klinger, 292 *Ill. App.* 321 (1937).
8. State v. Pratt, 92 *Wash.* 200, 158 *Pac.* 981 (1916).
9. People v. Cosper, 76 *Cal. App.* 597, 245 *Pac.* 466 (1926). State v. Mylod.[6]
10. People v. Gordon, 194 *Ill.* 560 (1902).
11. People v. Trenner, 144 *Ill. App.* 275 (1908).
12. People v. Vogelgesang, 221 *N. Y.* 290, 116 *N. E.* 977 (1917).
13. Regina v. Beer, 32 *Can. L. J.* 416 (1895).
14. Smith v. People, 51 *Col.* 270 (1911).
15. State v. Buswell.[5] State v. Marble.[5]
16. People v. Cole, 219 *N. Y.* 98, 113 *N. E.* 790 (1916).
17. Davis v. Beason, 133 *U. S.* 333 (1889).
18. Reynolds v. United States, 98 *U. S.* 145 (1878).
19. State v. Marble, 72 *Ohio St.* 21, 73 *N. E.* 1063 (1905).
20. 31 *C. J.* 1079. 14 *R. C. L.* 258.
21. State v. Chenoweth, 163 *Ind.* 94 (1904).
22. Oakey v. Jackson, *L. R.* 1 *K. B.* (1914) 216.
23. State v. Staples, 126 *Minn.* 396 (1914). Stehr v. State, 92 *Neb.* 755 (1913). State v. Barnes, 141 *Tenn.* 469 (1919).
24. 13 *R. C. L.* 858.
25. 29 *C. J.* 1159, 1160. 10 *A. L. R.* 1146. *Wharton on Homicide* (1907 ed.) No. 452. Queen v. Downes, *L. R.* 1 *Q. B. Div.* 25 (1875). State v. Sandford, 99 *Me.* 441, 59 *Atl.* 597 (1905). Rex v. Lewis, 6 *Ont. L. Rep.* 132, 1 *B. R. C.* 732 (1903). Commonwealth v. Hoffman, 29 *Penn. Co. Ct. Rep.* 65 (1903). Commonwealth v. Breth, 44 *Penn. Co. Ct. Rep.* 56 (1915). Rex v. Brooks, 9 *B. C. R.* 13 (1902). Queen v. Senior, *L. R.* 1 *Q. B. Div.* (1899) 238. State v. Chenoweth, 163 *Ind.* 94 (1904). Kansas City v. Baird, 92 *Mo. App.* 204 (1902). Queen v. Morby, *L. R.* 8 *Q. B. Div.* 571 (1882).
26. Queen v. Senior, *L. R.* 1 *Q. B. Div.* (1899) 283.
27. Rex v. Lewis, 6 *Ont. L. Rep.* 132, 1 *B. R. C.* 732 (1903).
28. People v. Pierson, 176 *N. Y.* 201, 68 *N. E.* 243 (1903).
29. 10 *A. L. R.* 1139.
30. Commonwealth v. Hoffman, 29 *Penn. Co. Ct. Rep.* 65 (1903).
31. Commonwealth v. Breth, 44 *Penn. Co. Ct. Rep.* 56 (1915).
32. Rex. v. Brooks, 9 *B. C. R.* 13 (1902).
33. Rex. v. Elder, 35 *Manitoba* 161, 44 *Can. Crim. Cas.* 75 (1925). Regina v. Beer. 32 *Can. L. J.* 416 (1895).
34. State v. Karsonky, 197 *Wash.* 87, 84 *Pac.* (2) 390 (1938).

MEDICAL PROGRESS

UNCOMMON INFECTIOUS DISEASES IN NEW ENGLAND*

CHESTER S. KEEFER, M.D.†

BOSTON

SINCE 1921, several infectious diseases have been recognized with increasing frequency in the United States. These include rat-bite fever, rickettsial diseases, Weil's disease, tularemia and brucellosis. Inasmuch as all these infections have been encountered in New England during the past few years, it seems proper and fitting that a few of the more important features and advances that have been recorded recently should be reviewed at this time.

Haverhill and Rat-Bite Fevers

In 1926, Place, Sutton and Willner[1] described an epidemic of illness in Haverhill, Massachusetts, which was characterized by fever, a skin eruption and arthritis. Parker and Hudson[2] isolated from the circulating blood and joints of these patients an organism that was found to be identical with *Streptobacillus moniliformis,* which had been isolated independently from a single case by Levaditi, Nicolau and Poincloux.[3] The blood of patients recovering from this disease also contained agglutinins against this particular organism. Previous to these observations Schottmüller,[4] Blake[5] and others had described a form of rat-bite fever in man that resembled in many respects the clinical features of the cases reported by Place, Sutton and Willner,[1, 6] and the organisms isolated from these cases were similar to those obtained from the latter. More recently, organisms identical with those described in so-called "Haverhill fever" have been isolated from infections following rat bites in man[7, 8]; and they have also been found in the arthritis of spontaneous polyarticular rheumatism in mice.[9, 10] It seems clear, then, that mice and rats harbor this organism in their mouths, and that they may suffer from a form of arthritis as a re-

*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Wade Professor of Medicine, Boston University School of Medicine; director, Evans Memorial, Massachusetts Memorial Hospitals.

sult of the infection. Moreover, following the bite of a rat, a form of rat-bite fever may develop in man that may resemble in all respects Haverhill fever.

One of the curious features about the Haverhill epidemic was the fact that it was thought to be due to the ingestion of infected milk; it is possible that the milk had become contaminated from a milker, since the first person known to have had the disease was found on a farm supplying raw milk to the community that was subsequently involved in the illness. It was also discovered that one cow on his farm had agglutinins in the blood against the organism causing the disease; however, the cow was disposed of before additional examinations could be made. It was suggested, of course, that the milk might have been infected from contact with rats and mice or even a human case. However, another possibility must certainly be considered in the future, namely, the occurrence of this organism or of one closely related to it in cows' milk.

In 1935, Klieneberger[11] was able to demonstrate a "pleuropneumonia-like organism" in all cultures of *S. moniliformis*. These organisms were designated as "L forms," and she considered them to be natural symbionts in all infections due to *S. moniliformis*. Other students of this organism have confirmed Klieneberger's valuable observations, but there have been several dissenting views concerning the interpretation of the significance of the L forms. Instead of accepting the interpretation of L forms as being due to distinct organisms, and therefore symbionts, it has been suggested that they are variants of the streptobacillus.[8, 12] This matter requires further study, but if it can be demonstrated that organisms resembling those causing pleuropneumonia in cattle can be converted into streptobacilli, the possibility of human infection from milk becomes much more significant. Thus it may be seen that pleuropneumonia in cattle or *S. moniliformis* infection in rats or mice may be the sources of infection for a form of rat-bite fever in man or for cases of Haverhill fever. The clinical differences may be due to the portal of entry of the organism. To avoid confusion, it is suggested that these cases be called *S. moniliformis* infections rather than rat-bite fever or Haverhill fever.

It is well in any patient who has fever, skin eruption and arthritis to consider the possibility of *S. moniliformis* infection. If there has been a history of a recent bite by a mouse or a rat, or of the ingestion of raw milk, the diagnosis becomes likely. It can be established with certainty by isolating the organism from the blood or synovial fluid or by detecting agglutinins in the circulating blood.

Rickettsial Diseases

Typhus and Rocky Mountain Spotted Fever

One of the major advances in the study of typhus and Rocky Mountain spotted fever during the last year was the announcement by Zinsser, Plotz and Enders[13] of a method for producing vaccine on a large scale. Cox and Bell[14] have also developed a vaccine that is effective in protecting animals. These vaccines will undoubtedly be subjected to clinical trial, and the results will be awaited with interest.

The development of antiserum against rickettsial diseases continues to attract attention, and progress has been reported by Topping.[15] It is quite possible that the use of large amounts of antiserum in the treatment of these diseases will definitely reduce the fatality rate.

It is becoming increasingly clear that typhus and Rocky Mountain spotted fever are present in various parts of the United States. Welch and Jakmauh[16] and Campbell and Ketchum[17] have reported cases of Rocky Mountain spotted fever in New England, and cases are now recognized along the eastern seaboard with increasing frequency. Campbell and Ketchum pointed out that there are no essential clinical differences between the Eastern and the Western varieties of Rocky Mountain spotted fever, and Topping and Dyer[18] have isolated the Western strain in the eastern part of the United States, so that it would be advisable to classify cases on the basis of virulence or of behavior in guinea pigs rather than according to geography and clinical type.

Typhus or Rocky Mountain spotted fever should be suspected in any patient who has the symptoms and signs of an acute infection with a skin eruption, especially if there are symptoms and signs referable to the brain and meninges, and congestion of the conjunctivas. If one remembers that rickettsial diseases caused widespread damage and lesions of the capillaries, especially of the brain, meninges and skin, and in this way cause anatomic damage, it is much easier to understand the symptoms and signs. All patients suspected of having either disease should be questioned for the possibility of tick bites, or at least contact with ticks. The Weil-Felix test, which becomes positive between the eleventh and nineteenth days, usually establishes the diagnosis.

American Q Fever

The recent studies of Hornibrook and Nelson[19] and Dyer, Topping and Bengtson[20] of an outbreak of pneumonitis, which was identified as being due

to the rickettsia of American Q fever, are among the most interesting and valuable contributions to the study of infectious diseases this year.

During the last five years, there has been an increasing interest in a group of infections characterized by bronchopneumonia of indeterminate duration, and various other clinical features such as skin eruption, pericarditis, hematuria, enlargement of the liver, spleen and lymph nodes, jaundice, migratory arthritis and encephalitis. Excellent clinical descriptions of this disease are available in the papers of Murray,[21] Kneeland and Smetana,[22] Longcope[23] and Reimann.[24] Efforts have been made to isolate a virus or other infective agents from the blood and exudates of these cases without conclusive results. For this reason the recent report[19] of the finding of rickettsia among a group of 15 patients with pneumonitis has excited widespread interest. The epidemic occurred among workers in one building of the National Institute of Health in Washington in the spring of 1940. The rickettsia of Q fever was isolated from 3 of these cases, in 2 from the blood and in 1, which was fatal, from the spleen. From the epidemiologic studies there was no convincing evidence that either personal contact or the intervention of an insect vector was responsible for the transmission of the disease.

These observations should serve as a stimulus for further investigation of cases of pneumonitis in other parts of the country to determine whether the same agent is responsible for the disease elsewhere.

Weil's Disease

Cases of Weil's disease are being recognized with increasing frequency in the United States, England by Jeghers, Houghton and Foley,[26] and Proger[27] has observed a case in his own practice.

The recognition of Weil's disease depends on the isolation of the *Leptospira icterohaemorrhagiae* from the blood or urine of the patient by means of inoculation of susceptible animals and on the appearance of specific agglutinins in the blood plasma. The first step in the diagnosis, however, is to consider the possibility in cases of obscure infection with or without jaundice, especially if there is an associated severe myalgia, nephritis, hemorrhages into the skin, conjunctivitis or aseptic meningitis. Such a possibility becomes strengthened if the patient is a sewer worker, fish-handler, slaughterhouse worker or miner, is known to have been swimming in stagnant or polluted water or has lived or worked in rat-infested premises. Persons who fall into the canals of Holland frequently develop the disease.

The clinical features of Weil's disease vary widely, depending on the severity of the infection; for purposes of description they may be divided into three stages, although some patients may not show any of the features characteristic of the second and third stages. The first stage is characterized by the sudden onset of all the symptoms of an acute infection, — fever, chills, nausea, vomiting, pain in the muscles, especially of the calves, conjunctivitis and herpes, — with leukocytosis. In a few patients all the signs of meningitis appear.[28] If the patient recovers within a few days after the onset of the illness, and does not develop jaundice, the diagnosis may never be established unless the possibility of the disease is considered and agglutination tests are carried out.

About half the cases go on to the second stage, in which jaundice appears and may be intense and associated with hemorrhages into the skin and from the mucous membranes of the nose and gastrointestinal tract; there may also be hematomas. The third stage, which frequently appears within the third week, is characterized by fever and, in some cases, nephritis. The various stages and the clinical course are shown in Table 1.

Table 1. *Summary of Clinical and Laboratory Findings in Various Stages of Weil's Disease.*

Findings	Incubation Period (4–19 Days)	First Stage (4–7 Days)	Second Stage (7–10 Days)	Third Stage (10–21 Days)
Clinical	None	Fever, chills, muscle pains, nausea and vomiting, meningeal signs, conjunctivitis, herpes labialis hemorrhagica	Jaundice (50 per cent), enlarged liver, hemorrhages and signs of nephritis (commonest in patients with jaundice)	Fever,* nephritis
Laboratory	None	Leukocytosis (rarely above 20,000), spirochetes in blood and urine	Leukocytosis, icterus, nitrogen retention, spirochetes absent from blood but present in urine, antibodies present in blood	Spirochetes absent in blood and urine, antibodies present in blood

*The fever in 25 to 40 per cent of cases lasts 4 to 20 days.

and Blake[25] has recently reviewed the salient features of the disorder and collected all the reported cases. The case reported by Blake himself occurred in a dairyman who about ten days before the onset of the illness had been engaged in demolishing an old barn, which was infested with rats. Other cases have been reported in New

Tularemia

Tularemia is a rare disease in New England, only occasional cases having been reported. Badger[29] reported 1 case of the typhoidal form of the disease, and McKhann[30] observed 1. During the past year, Belding[31] has isolated *Pasteurella tularensis* from the organs of a rabbit in Massachusetts. Accordingly, physicians should be on the lookout for clinical cases of tularemia, especially during the hunting season. An excellent review of tularemia has been made by Foshay[32] during the past year, and this should be read in detail by those who are interested in the disease. A few of the salient features of the disease may be summarized as follows.

Tularemia, which is caused by infection with *Past. tularensis,* is usually acquired in human beings by contact with infected rabbits, squirrels, ticks or biting flies (deer flies). Other less common sources of infection are cat bites, and contact with dressed chickens that have become contaminated through handling by poultrymen who handle infected rabbits. Other animals that may serve as a source of infection for man are quail, opossum, pheasant, grouse, skunk, beaver and snapping turtle. Rare cases occur from personal contact or from handling infected pelts of rabbits. Laboratory infections have been noted, and eating infected, insufficiently cooked food is also a source.

The diagnosis of tularemia is made by isolating the organism from the circulating blood or foci of infection, or by detecting specific agglutinins in the blood plasma. The clinical features that naturally suggest the nature of the disease are: the constitutional symptoms and signs of infection; a local ulcerative (primary) lesion with satellite lymphadenopathy, usually of the skin of the upper extremities, face or conjunctiva (92 per cent); and the presence of metastatic lesions in the lungs and pleura (20 per cent). In 8 per cent of reported cases prolonged fever without local signs is the outstanding feature of the illness.

A typical history is as follows. After the dressing of a rabbit during the hunting season, the skin of the fingers is accidentally broken. For several days, usually two to five but varying from one to ten, there are no local or general signs of infection. Then there is a sudden departure from health, with fever and all the accompanying signs of infection.

At the site of the original injury an ulcerative lesion develops in about two thirds of the cases and attracts the attention of the patient and his physician. There is an associated enlargement of the regional lymph nodes. In the remaining third, the lymph nodes in the neighborhood of the original injury are first noticed to be enlarged. Visible lymphangitis is not common unless the infection is a mixed one. Nodular lymphangitis may be present in a few cases. Usually the primary lesion appears with the onset of the fever, but it may not develop for forty-eight hours after the onset. In some cases there is an initial bout of fever lasting from one to four days, which is followed by a remission of from one to five days, after which time the fever becomes elevated for a period ranging between two and four weeks. During this febrile period, signs of metastatic lesions in the lungs, liver, spleen or other organs may appear, so that the patient may develop the signs of pneumonia, pleural effusion, pyopneumothorax, pericarditis or enlargement of the liver or spleen, with or without jaundice.

In about half the cases, the lymph nodes suppurate, and they may break down as long as five months after the onset of the disease. Recurrent enlargement of the lymph nodes may occur as late as three months to three years after the initial infection. In the recurrent swellings of the lymph nodes, suppuration occurs in about half the cases, and the pus is commonly sterile.

Relapses may occur from eight months to two years after the onset of infection. The average duration of the infection is about four months. Local lesions last on an average about thirty days.

Death occurs in 6 to 10 per cent of cases. It is seen oftenest in patients over fifty years of age and in those with the septicemic form of the disease, or in persons with other debilitating diseases.

From the review and study of Foshay,[32] there is convincing evidence that serum treatment shortens the course of the disease. Serum must be given early and in adequate amounts (30 to 180 cc.). The evidence that chemotherapy shortens the course of the disease is still controversial.

Agglutination tests are the most reliable diagnostic tests. They usually become positive after the first ten days of the disease, but in some cases on record positive tests appeared as late as the fourth week. Once they appear, they are present for years.

Positive intradermal tests with the especially prepared antigens (organisms oxidized with nitrous acid) are commonly observed in the first week of the illness, before the agglutination tests become positive.

Brucellosis

In 1939, the second edition of Huddleson's[33] excellent monograph, *Brucellosis in Man and Animals,* was published. This is the most important

discussion of the subject in English during the last few years. Since 1924, this disease has been recognized in various parts of the United States with increasing frequency. Most physicians are familiar with its widespread existence, and attempts are being made to establish the diagnosis in all cases of prolonged unexplained fever.

The isolation of *Brucella abortus* from the circulating blood or from a localized area of suppuration establishes the diagnosis of brucellosis or undulant fever. In many cases, however, such isolation is impossible and it is necessary to rely on the clinical course of the disease, the agglutination reaction, skin tests and the opsonic index of the circulating polymorphonuclear leukocytes.

So far as is known, the infection arises oftenest from the ingestion of organisms with food. They gain entrance to the body through the gastrointestinal tract, and indirect evidence leads one to believe that they focalize in the liver, spleen, lymph nodes and other organs, where they may, in rare cases, set up areas of suppuration. Generally speaking, however, they do not produce abscesses, but local physical signs due to suppuration are by no means unknown. Areas of infection have been found in the bones and joints,—especially the spine and larger joints,—the meninges, the endocardium, the periosteum, the liver and spleen, the ovaries, the genitourinary tract and the blood vessels.

The infection usually occurs in persons who consume raw milk from infected cows, and in persons who handle infected material coming from cows, goats or pigs. Butchers, slaughterhouse men, farmers and veterinarians frequently have the disease in a latent form.

When the infective organisms are not isolated from the circulating blood or local areas of infection, the diagnosis may be suggested in a patient with low-grade or high, irregular fever, with moderate splenomegaly, without localizing signs of infection, with a normal or slightly increased leukocyte count and with an increase in the lymphocytes and mononuclear cells. In these cases, to establish a diagnosis one must use the other laboratory tests, the most useful of which is the agglutination reaction. An increase in the titer above 1:40, especially when the increase occurs as the disease advances, is of diagnostic significance. When the blood cultures and agglutination tests are negative, the use of the skin tests and the opsonic index may provide valuable indirect evidence of infection. A positive skin test may be present without a positive agglutination reaction, or with a negative opsonic index. This may be taken as an indication of hypersensitiveness to the products of *Br. abortus*, and it must be interpreted in the same way as a tuberculin reaction; that is, the positive test may indicate a previous or a present infection. When there is a positive opsonic index and a positive skin test in a patient with fever but without a positive blood culture or agglutination reaction, these tests have less diagnostic significance, since they indicate that the patient has developed sufficient antibodies in the past to allow phagocytosis of organisms and to show a reaction to the products of *Br. abortus* when injected into the skin.

Summing up these tests, it may be said that a positive blood culture is the most valuable. The agglutination test ranks second. A positive skin test with a negative opsonic index comes third. A positive skin test and opsonic index, without other evidence of infection by this group of organisms, is of little positive value in the diagnosis.

Since this infection tends to focalize in certain areas, the patient may come under observation with symptoms and signs of a focal infection, or once the diagnosis has been established, these focal infections may appear. The following clinical manifestations may suggest undulant fever: relapsing or undulating fever, which may be low grade or continuous with negative blood cultures, a moderate splenomegaly and a normal leukocyte count with an increase of the lymphocytes and monocytes; an infective spondylitis; an intermittent hydrarthrosis; a suppurative arthritis; an enlargement of the liver and spleen, with hematemesis; pelvic abscess; an abscess of the periosteum; an endocarditis; infective mycotic aneurysm of a large artery; a low-grade meningitis.

On the whole, the treatment of brucellosis is unsatisfactory. Chemotherapy with the various sulfonamide drugs has yielded results that are in many ways difficult to assess. A review of the effects, by Blumgart and Gilligan,[34] indicates that sulfanilamide has occasionally been effective. In many cases, however, the results are disappointing, since relapses are observed following an apparent remission induced by the drug. It is fair to say that no chemotherapeutic agent so far developed will be effective in all cases. Wainwright[35] has reported favorable results in some cases following the use of neoarsphenamine.

One form of treatment that has been used extensively is the injection of brucellin. The results in 100 cases have been summarized by Huddleson,[33] whose conservative statements warrant most careful consideration. He states that from his experience there is no doubt that the course of the disease may be shortened, provided certain procedures are followed and an adequate amount

of material is used. According to Huddleson, the course of the disease is altered "by producing a systemic allergic reaction which in turn is accompanied by a neutrophilic leukocytosis and increase in immune opsonins." It is also his opinion that the efficiency of brucellin depends on the existence and continuation of a state of sensitization in the patient under treatment. The absence of a state of sensitization at the beginning of treatment or its disappearance during treatment will be followed by poor results following the use of brucellin. It is for these reasons that the dose must be varied from one patient to another. Those who are interested in this method of treatment should consult Huddleson's monograph.

78 E. Concord Street

References

1. Place, E. H., Sutton, L. E., Jr., and Willner, O. Erythema arthriticum epidemicum: preliminary report. *Boston M. & S. J.* **194**:285-287, 1926.
2. Parker, F., Jr. and Hudson, N. P. The etiology of Haverhill fever (erythema arthriticum epidemicum). *Am. J. Path.* **2**:357-379, 1926.
3. Levaditi, C., Nicolau, S. and Poincloux, P. Recherches sur l'étiologie de l'érythème polymorphe aigue son agent étiologique: *Streptobacillus moniliformis*. *Presse méd.* **34**:340-343, 1926. Sur le rôle d'étiologie du *Streptobacillus moniliformis* dans l'érythème polymorphe aigue septicemique. *Compt. rend. Acad. d. sc.* **180**:1188-1190, 1925.
4. Schottmüller, H. Aetiologie und Klinik der Biszkrankheit. *Ergänzungsheft zu Dermat. Wchnschr.* **58**:77-103, 1914.
5. Blake, F. G. The etiology of rat-bite fever. *J. Exper. Med.* **23**:39-60, 1916.
6. Place, E. H. and Sutton, L. E. Erythema arthriticum epidemicum (Haverhill fever). *Arch. Int. Med.* **54**:659-684, 1934.
7. Scharles, F. H. and Seastone, C. V. Haverhill fever following rat-bite. *New Eng. J. Med.* **211**:711-714, 1934.
8. Dawson, M. H. and Hobby, G. L. Rat-bite fever. *Tr. A. Am. Physicians* **54**:329-332, 1939.
9. Levaditi, C., Selbie, F. R. and Schoen, R. Les arthrites du rheumatisme polyarticulaire spontané de la souris provoqué par le *Streptobacillus moniliformis*. *Compt. rend. Soc. de biol.* **103**:1193-1197, 1930.
10. Levaditi, C. and Selbie, F. R. Mode de transmission de l'érythème polymorphe aigue epidemique. *Compt. rend. Acad. d. sc.* **189**:1332, 1929.
11. Klieneberger, E. The natural occurrence of pleuro-pneumonia-like organisms in apparent symbiosis with *Streptobacillus moniliformis* and other bacteria. *J. Path. & Bact.* **40**:93-105, 1935. Further studies on *Streptobacillus moniliformis* and its symbiont. *Ibid.* **42**:587-598, 1936.
12. Dienes, L. and Edsall, G. Observations on the L-organism of Klieneberger. *Proc. Soc. Exper. Biol. & Med.* **36**:740-744, 1937.
    Dienes, L. Further observation on the L organism of Klieneberger. *Ibid.* **39**:365-367, 1938.
13. Zinsser, H., Plotz, H. and Enders, J. F. Mass production of vaccine against typhus fever and of the European type. *Science* **91**:51, 1940.
14. Cox, H. R. and Bell, E. J. Epidemic and endemic typhus: protective value for guinea pigs of vaccines prepared from infected tissues of the developing chick embryo. *Pub. Health Rep.* **55**:110-115, 1940.
15. Topping, N. H. Treatment of infected laboratory animals with immune rabbit serum. *Pub. Health Rep.* **55**:41-46, 1940.
16. Welch, N. A. and Jakmauh, P. J. Rocky Mountain spotted fever: a case report. *New Eng. J. Med.* **221**:937-939, 1939.
17. Campbell, E. P. and Ketchum, W. H. Rocky Mountain spotted fever: an analysis of seven cases, including one laboratory infection. *New Eng. J. Med.* **223**:540-543, 1940.
18. Topping, N. H. and Dyer, B. E. A highly virulent strain of Rocky Mountain spotted fever virus isolated in the eastern United States. *Pub. Health Rep.* **55**:728-731, 1940.
19. Hornibrook, J. W. and Nelson, K. R. An institutional outbreak of pneumonitis. I. Epidemiological and clinical studies. *Pub. Health Rep.* **55**:1936-1954, 1940.
20. Dyer, R. E., Topping, N. H. and Bengtson, I. A. An institutional outbreak of pneumonitis. II. Isolation and identification of causative agent. *Pub. Health Rep.* **55**:1945-1954, 1940.
21. Murray, M. E. Atypical bronchopneumonia of unknown etiology possibly due to filterable virus. *New Eng. J. Med.* **222**:565-573, 1940.
22. Kneeland, Y., Jr. and Smetana, H. F. Current bronchopneumonia of unusual character and undetermined etiology. *Bull. Johns Hopkins Hosp.* **67**:229-267, 1940.
23. Longcope, W. T. Bronchopneumonia of unknown etiology (variety X): a report of thirty-two cases with two deaths. *Bull. Johns Hopkins Hosp.* **67**:268-305, 1940.
24. Reimann, H. A. An acute infection of the respiratory tract with atypical pneumonia: disease entity probably caused by filtrable virus. *J. A. M. A.* **111**:2377-2384, 1938.
25. Blake, F. G. Weil's disease in the United States: report of a case in Connecticut. *New Eng. J. Med.* **223**:561-565, 1940.
26. Jeghers, H. J., Houghton, J. D. and Foley, J. A. Weil's disease: report of a case with postmortem observations and review of recent literature. *Arch. Path.* **20**:447-476, 1935.
27. Proger, S. H. personal communication.
28. Lemierre, A. *Maladies infectieuses.* 309 pp. Paris: Masson & Cie, 1937. P. 73.
29. Badger, T. L. Tularemia: report of a case of typhoidal form. *New Eng. J. Med.* **220**:187-191, 1939.
30. McKhann, C. F. personal communication.
31. Belding, D. S. personal communication.
32. Foshay, L. Tularemia: a summary of certain aspects of the disease including methods for early diagnosis and the results of serum treatment in 600 patients. *Medicine* **19**:1-83, 1940.
33. Huddleson, I. F., Hardy, A. V., Debono, J. E. and Giltner, W. *Brucellosis in Man and Animals.* 339 pp. New York: The Commonwealth Fund, 1939. Pp. 136-138.
34. Blumgart, H. L. and Gilligan, D. R. The treatment of undulant fever with sulfanilamide and related compounds. *M. Clin. North America* **23**:1193-1203, 1939.
35. Wainwright, C. W. Melitensis infection: treatment with neoarsphenamine. *South. M. J.* **30**:600-608, 1937.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27061

PRESENTATION OF CASE

A fifty-year-old housewife entered the hospital complaining of hematemesis.

Approximately a year and a half before entry the patient developed a vague sense of epigastric pressure unaccompanied by other symptoms and relieved by a slight adjustment of her corset in the form of padding at the upper edge. Three months before admission, over a period of several weeks, she noticed that food sometimes seemed to "catch" in her throat. There was no pain, and with a drink of water the food passed on. No other symptoms appeared until one night, six weeks before entry, the patient awoke feeling as though she were "floating on air." In addition, she felt nauseated and suddenly vomited about one pint of bright-red blood. This incident did not recur, but since then she had suffered from slight anorexia, weakness, easy fatigability, and shortness of breath on exertion. Her stools were black for four weeks thereafter. Following the hematemesis, her physician instituted a dietary regimen of milk and cream for two weeks, then strained vegetables and riced foods, with a bismuth powder after each meal. The patient had not lost weight. At no time did she have postprandial pain, dyspepsia, colic, constipation, diarrhea, jaundice, food intolerance or swelling of the abdomen or legs. There was no history of excessive alcoholic consumption.

The patient had had pertussis at forty, and twelve years before admission a "broken-down gland" in the right posterior neck, which was drained and healed readily. The family history was noncontributory.

On examination the patient was well developed and well nourished and in no apparent distress. Examination of the heart and lungs was negative; the blood pressure was 118 systolic, 80 diastolic. The abdomen was tender in the midepigastrium. Vaginal examination showed a parous introitus and leukorrhea. The cervix was large and badly lacerated with marked erosions. The uterus was retroverted; the fundus was not felt, and the vaults were clear. Rectal examination was negative.

The temperature, pulse and respirations were normal.

Examination of the urine was negative. Examination of the blood showed a red-cell count of 4,500,000 with a hemoglobin of 55 per cent, and a white-cell count of 7600 of which 53 per cent were polymorphonuclears. A blood Hinton test was negative.

The nonprotein nitrogen of the blood serum was 21 mg. per 100 cc., the chlorides 108.1 milliequiv. per liter and the serum protein 6.0 gm. per 100 cc. The vitamin C level was 1 to 2 mg. per 100 cc. A gastric analysis showed 20 cc. N/10 free hydrochloric acid, with a total acidity of 37 cc. after injection of histamine. Examination of the stools was negative.

A gastrointestinal series showed a 7.5-by-5-cm. mass arising from a broad base on the lesser curvature and posterior wall of the fundus of the stomach. The base of the tumor lay just posterior to the cardia. The surface of the mass was rather smooth, but slightly lobulated, and one deep crater-like depression was seen in its lateral portion. There was only a slight shift in the position of the mass when the patient was upright. The rest of the stomach showed no evidence of disease.

The patient was given vitamins and a 600-cc. blood transfusion. On the fifth hospital day a gastroscopic examination was performed. The instrument passed readily into the cardia; there was no evidence of disease in the esophagus, and the cardiac orifice appeared normal. The instrument was then passed a few centimeters inside the cardiac orifice, where a smooth gastric mucosa without normal gastric rugae was seen. It was not possible to be sure whether this was normal gastric mucosa or neoplasm, and hence no biopsy was taken. There was a small amount of bleeding, and because of this, gastroscopy with the flexible tube was postponed. The following day this procedure was repeated. The pylorus was well visualized and appeared normal, as did the antrum; peristalsis was normal. In the upper part of the body in the five o'clock position there was a smooth, rounded, elongated submucosal tumor that appeared to be approximately 5 by 7 cm. in diameter and elevated 1 to 1.5 cm. above the surrounding mucosa. There was no visible break in the mucosa overlying the tumor. Near its base the rugae started to pass over the tumor, but were gradually flattened out. The mucosa surrounding the lesion was markedly atrophic, with clearly visible vessels shining through. The tumor appeared to extend to within 1 cm. of the cardia without involving it. Another 600-cc. blood transfusion was given, and on the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Arthur W. Allen: In some ways I hesitate to have Dr. Holmes show us these x-ray films, because if the films bear out the description we have here in the text it brings the diagnosis down to one type of lesion. However, we shall see how difficult he can make it by his interpretation of the films.

Dr. George W. Holmes: The surprising thing is that some films show practically nothing abnormal and others show a very definite lesion. I presume that the latter present the correct picture, and I shall interpret them about as described in the record. There is a large smooth lobular mass in the fundus of the stomach with a well-defined crater in its center, a picture characteristic of one particular tumor. I suppose it is the same one you have in mind.

Dr. Allen: Dr. Edward B. Benedict's description of this tumor confirms Dr. Holmes's interpretation.

We have, then, a patient with massive hemorrhage from the upper gastrointestinal tract.[1] According to the records in this hospital, this must fall into one of eight categories. The commoner causes of sudden massive hemorrhage are posterior-wall duodenal ulcer, gastric ulcer, gastrojejunal ulcer, esophageal varices, carcinoma of the stomach, hypertrophic gastritis, polyposis and leiomyoma. In this case we can rule out many of these lesions. We have no reason whatever to suspect the duodenum. We have no reason to suspect that this hemorrhage came from esophageal varices. The gastroscopist did not find gastritis. I do not believe that this is polyposis, because usually the polyps are multiple and do not show such a broad base as this tumor appears to have.

We do have to consider certain possibilities other than what I believe to be the obvious diagnosis. One cannot always be sure that a tumor, however smooth, however apparently submucosal, is not carcinomatous. Carcinomatous tumors are nearly always ulcerated, or if not ulcerated, they involve a much larger portion of the stomach than this one does. It is noteworthy that this tumor does not have a large ulcer crater, despite the presence of free hydrochloric acid in the stomach. We have recently reviewed all the gastric ulcers treated here in the past ten years and were much surprised to find what a high incidence of cancer there was in these patients beyond middle life, with a short story of indigestion. A person beyond middle life who has a gastric lesion with a short history has five times as much chance to have cancer as ulcer. We treat too many gastric ulcers conservatively, and let them get away from us only to return in an inoperable state with obvious cancer. I think we can rule out such a possibility in this particular patient.

The tumors that are submucosal and that have a smooth surface as demonstrated both by x-ray and gastroscopy are apt to belong to the leiomyoma group. The majority of the patients who enter this hospital with leiomyoma of the stomach enter with massive hemorrhage, and most of them have a preliminary diagnosis of inoperable cancer when they get here. This location is not an uncommon one for leiomyoma. Two of the cases I have done have been so near the cardia on the posterior wall that to get them out without total gastrectomy the operation had to be done through an opening in the anterior wall of the stomach. Others have been found in various locations in the stomach, and the majority have been treated by partial gastrectomy. If one knew which of these tumors were benign, and a certain percentage of them seem to be entirely benign, one might get away with a local excision. In one of my cases that I did through the stomach, a smaller tumor than this one, the patient is alive and well after six years, with no evidence of recurrence. Another patient died four years after operation with jaundice and a palpable liver, so that although there was no autopsy confirmation, it is fair to assume recurrence. Quite a large percentage of them are malignant. They show sarcomatous degeneration and are usually termed leiomyosarcomas. Recently Ransom,[2] of the University of Michigan, reported on tumors of neurogenic origin in the abdomen, and about 8 of the 20 cases presented tumors of the stomach that looked grossly very much like the one that we are discussing today. Coller[3] in discussing Ransom's paper called attention to the fact that if the histology of these tumors were more carefully reviewed more of them would be found to be of neurogenic origin.

The ulcer crater in the center of this smooth round tumor is characteristic of both the leiomyomatous and the neurogenic tumors. If one gets the specimen out one finds that the crater leads directly into a large blood vessel from which the hemorrhage comes.

One should mention the possibility of lymphoma in dealing with any intra-abdominal tumor, particularly one that is tender. So far as I know, I have not had the experience of seeing a lymphomatous lesion of the stomach that was admitted on account of massive hematemesis. In going over our ulcerative gastric lesions in the past ten years, we found only one benign tumor arising from the fundus of the stomach, and that was due to syphilis. This woman had a negative Hinton test, and nothing else about this case sug-

gests syphilis. Therefore, I shall make a diagnosis of leiomyoma of the stomach, possibly with sarcomatous degeneration, possibly a tumor of neurogenic origin.

DR. TRACY B. MALLORY: Are there any other suggestions? Dr. Homans, should you care to comment?

DR. JOHN HOMANS: No.

DR. MALLORY: Dr. Homans had a case very much like this some years ago that I remember reviewing. I was at that time interested in leiomyomas of the stomach, and a case at the Peter Bent Brigham Hospital was called to my attention. It seemed to me at first glance to be very typical, but Dr. Homans made a remark which I have not forgotten and which has influenced my thinking about these tumors ever since. He said, "I should be very cautious about accepting that as a leiomyoma, because she came back four years later with an intraspinal tumor, which Dr. Cushing removed. You had better be sure it is not a neurogenic fibrosarcoma."

DR. HOMANS: I remember the patient.

CLINICAL DIAGNOSIS

Leiomyoma of stomach.

DR. ALLEN'S DIAGNOSIS

Leiomyoma of stomach, with possible sarcomatous degeneration?

Neurogenic fibrosarcoma of stomach?

ANATOMIC DIAGNOSIS

Neurogenic fibrosarcoma of the stomach.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was operated on by Dr. Edward D. Churchill; I am sorry he is not here to describe his operation. Because of the very high location, he decided to approach the tumor through the transpleural route. That was done, and it was found that the tumor was in the fundus, far enough separated from the mouth of the esophagus to do a fundusectomy, close up the stomach and leave it in continuity with the esophagus. The patient made a very successful recovery and was discharged on the sixteenth postoperative day, completely relieved. The tumor was of about the size described in the x-ray reports and did show central ulceration. In contrast to a leiomyoma, which after all is nothing but a fibroid, this tumor was quite soft, and appeared very edematous and vascular. On microscopic examination it is evident that it is a spindle-cell sarcoma growing at a moderate rate of speed, with fairly numerous mitotic figures, but no multinucleated giant cells or other evidence of a high degree of malignancy. Further diagnosis of the tumor rests on the minute histologic character, and I am not sure if it were shown to a group of pathologists that they would give a unanimous opinion. I should classify it as a neurogenic fibrosarcoma, not as a leiomyosarcoma. In sections stained with phosphotungstic acid the normal muscle of the stomach wall showed good myoglia fibrils, whereas I could demonstrate none in the tumor cells.

I wonder, Dr. Allen, if it would have been possible to have handled this case as satisfactorily with an approach from below.

DR. ALLEN: Being an abdominal surgeon I should have taken it out from below. I think that a shoemaker must stick to his last. We saw a case this morning on grand rounds, a carcinoma of the stomach involving, we thought, the lower end of the esophagus, and I suggested to Dr. Churchill that it would be a good case to do transthoracically, whereupon he said, "Well for the sake of argument, why not approach it from the abdomen?" Either approach is satisfactory.

REFERENCES

1. Allen, A. W. Acute massive bleeding from upper gastro-intestinal tract. *Internat. Clin.* 4:205-223, 1937.
2. Ransom, H. K. and Kay, E. B. Abdominal neoplasms of neurogenic origin. *Ann. Surg.* 112:700-746, 1940.
3. Coller, F. A. discussion of Ransom and Kay.[2]

CASE 27062

PRESENTATION OF CASE

A sixty-year-old man entered the hospital complaining of bronchitis and fatigue of eight years' duration.

The patient stated that for twenty years he had suffered from chronic constipation with gaseous eructations after meals and for the eight years before entry from bronchitis occurring each winter, with a daily production of half a cupful of greenish-yellow sputum. In addition, for the previous three years he had noticed anorexia, weakness, easy fatigability and lack of energy as well as moderate dyspnea on exertion and slight orthopnea, but no edema or paroxysmal nocturnal dyspnea. Six weeks before admission he suffered an attack of "bronchitis" with slight fever, and a mild cough with a small amount of sputum. Since then he had noticed that his sputum was blood streaked. Two weeks before admission the patient had a chill with fever, and developed a pain in his left chest. He went to bed, weak and exhausted with generalized aching, and complained of dyspnea, an increase in coughing and bloody sputum. There was no palpitation, peripheral

edema or weight loss, but he had a few night sweats. Furthermore, he complained of difficulty in starting urination, with dribbling and nocturia once or twice a night for an unstated period. At the time of admission he was raising small amounts of bloody, apparently purulent sputum.

On examination the patient was well developed and well nourished, lethargic, extremely uncooperative, flushed, slightly cyanotic and apparently ill. The brachial and temporal arteries were tortuous. The heart was moderately enlarged to the left, with a bifid apical impulse. The sounds were rapid and of poor quality with a presystolic gallop rhythm; the blood pressure was 138 systolic, 80 diastolic. Examination of the lungs revealed slight dullness to percussion at both bases; the diaphragmatic excursion was normal. There were many coarse crackling rales in the left axilla, and anteriorly and posteriorly at the left base. A few rales were heard at the right base. Examination of the abdomen was negative except for an easily reducible right inguinal hernia in the scrotum. The prostate was enlarged, smooth, soft and tender. Examination of the nervous system was negative.

The temperature was 101°F., the pulse 100, and the respirations 30.

Examination of the urine showed a ++ test for albumin. Examination of the blood showed a red-cell count of 5,060,000 with a hemoglobin of 100 per cent, and a white-cell count of 13,800 with 82 per cent polymorphonuclears. A blood Hinton test was negative. A gastric analysis gave a total fasting level of 2 cc. of N/10 hydrochloric acid per 100 cc., and a level of 6 cc. half an hour after the injection of histamine; there was no free acid, and a guaiac test was negative. The vital capacity of the lungs was 2000 cc. Examination of the stools was negative.

X-ray films of the chest showed a small amount of fluid in the left pleural cavity. The space between the gas bubble in the stomach and the diaphragm was unusually large, and there was a slight irregularity of the fundus of the stomach. The lung fields on both sides contained a number of rather poorly defined, approximately round areas of increased density measuring up to 2 cm. The heart was markedly increased in size, particularly to the left. The aorta was tortuous and slightly dilated.

A gastrointestinal series showed the esophagus to be normal. The deformity of the fundus previously described was seen to be produced by downward displacement of the fundus and not by intrinsic disease of the stomach. The downward displacement was apparently due to a slightly enlarged spleen. There was no evidence of intrinsic disease of the upper gastrointestinal tract.

An electrocardiographic recording showed normal rhythm at 105, a PR interval of 0.18 second and a prominent P_2. The QRS complex was widened up to 0.08 second, with slurring and splintering. There was slight depression of ST_1 and ST_2, and elevation of ST_3 and ST_4. T_1 was slightly inverted, T_2 low.

The patient was given digitalis and one 2-cc. dose of mercupurin and appeared to improve satisfactorily, becoming more alert and co-operative. Four days after admission the temperature dropped to normal, the white-cell count to 10,000. X-ray examination of the chest showed the lesions to be slightly smaller than at the last examination. There was still a small amount of fluid in the left pleural cavity, and the heart was still enlarged, though slightly smaller. On the seventh hospital day marked tenderness was noticed in the left calf, with cordlike masses suggestive of thrombosed veins. Two days later the dullness and rales at the left lung base had disappeared, but the heart rate still averaged 100. Later that day the patient was found dead in bed.

Differential Diagnosis

Dr. Edward F. Bland: I suspect several pathologic conditions were found in this patient, but I think that the principal diagnosis involves an explanation for the cough, sputum, hemoptysis and sudden exitus. He was sixty years old, had had so-called "winter bronchitis" for a number of years, and had raised a fair amount of sputum. I assume that this annual winter bronchitis represented a low-grade pulmonary infection, with perhaps slight structural alterations in the bronchial tree. In addition, in view of what comes later, perhaps there had also been an element of circulatory weakness. The evidence — marked cardiac enlargement, a gallop rhythm indicating serious weakness and an abnormal electrocardiogram — seems to show clearly that on admission he had significant cardiac disease. There is nothing, however, in the story that particularly suggests a recent acute change in the heart. Furthermore, the patient appeared to improve on digitalis. We must therefore assume that he had serious cardiac disease, presumably on a coronary basis. He had no known hypertension, and we can be reasonably certain that he did not have valvular disease. I think his heart may have been of some importance in the final events, but not the chief cause of his exitus. Finally, he had benign hyperplasia of the prostate, which appears not to have had much bearing on his final illness. So much for the background of his illness.

It seems to me that the central problem involves the final illness, and the findings in the lungs are probably most important. I wonder if we might see the x-ray films now. I take it that the gastrointestinal tract was examined with such zeal because of the original chest film, which showed the gas bubble in the stomach not quite so close to the diaphragm as it should be. Otherwise, I think one might have hesitated to pass a stomach tube into a patient as sick as he appeared to be.

Dr. George W. Holmes: The increase in the distance between the gas bubble and the diaphragm is not positive evidence of any pathologic lesion, but is worth taking note of. The complete absence of abnormality of the mucosal folds in the fundus rules out, I think, tumor in this part of the stomach. The widening of the space may be due to distortion of the picture, or as pointed out in the record, to enlargement of the spleen. The most obvious finding in the chest films is the enlargement of the heart. The enlargement is general, perhaps a little more to the left than to the right, and the border of the left ventricle is prominent. It was stated in the report that the aorta was somewhat dilated as well as tortuous. I think that the dilatation was very slight, if existent at all. I do not believe he had syphilitic aortitis, or the marked dilatation we sometimes see with hypertension. The description of the lungs is a little misleading, because it gives the impression that the lesions might have been due to metastatic cancer. To me they do not look that way. The general thickening of the lung markings throughout the chest and the haziness on the right side might have been due to pleuritis, but in general the picture looks more like localized atelectasis, pulmonary infarct, acute respiratory infection or something of that sort.

Dr. Bland: There is not much evidence of congestion?

Dr. Holmes: No; that is not the picture of congestive failure.

Dr. Bland: The mediastinum looks all right?

Dr. Holmes: Yes.

Dr. Bland: In general when a patient of this age comes in coughing and raising sputum, with fever and hemoptysis, one would like to know what the sputum shows microscopically, and I think we can assume that it was not remarkable, since nothing was said about it. Certainly the course of the illness does not suggest either tuberculosis or pneumonia. After seeing the x-ray films, I think we can discard tuberculosis. I considered cancer at some length from the written report of the x-ray studies, but after seeing the films I am inclined to discard that without serious consideration because the patient was in fairly good general condition, certainly not emaciated. The red-cell count was not down, and the onset of the disease does not particularly suggest a malignant lesion of the lung, either primary or secondary. I suppose, as noted previously, that the gastrointestinal tract was investigated so carefully because of the suggestion in the first chest films, but there was certainly no indication of disease from later x-ray study of the gastrointestinal tract or from examination of the stools. The patient probably did not have a tumor of the lung, either carcinoma or lymphoma. One can occasionally get hemoptysis with lymphoma, but it is very rare. Metastatic carcinoma of the lungs can rarely cause hemoptysis, but hemoptysis in the presence of cancer suggests primary bronchiogenic carcinoma.

Finally, we come to a consideration of what I think seems most likely; namely, that he had, complicating his heart disease and perhaps his chronic mild bronchiectasis, multiple pulmonary emboli with infarction. From the written description of the films, it seemed to me that either cancer or infarction of the lungs might be present. After seeing the films, there can be little doubt about the infarction. There was a good background for it. There is clear evidence of serious heart disease and some circulatory weakness, as shown by the gallop rhythm. The patient had a mild infection, to begin with, a chill, which usually means infection, and probably took to bed, which favored the development of deep phlebitis. Toward the end of his illness, signs of superficial phlebitis appeared in the veins of the left calf. Then we come to the sudden exitus interrupting his apparent improvement. We are on uncertain ground when we attempt to interpret the exact cause of death. He had serious cardiac disease, and something abrupt may have happened in connection with the heart, for example, ventricular fibrillation. Dr. Mallory may not find an obvious cause. On the other hand, since we are dealing with recurring pulmonary infarcts and obvious disease of the veins in one leg, it is somewhat likelier that he had a terminal pulmonary embolus.

Dr. William B. Breed: It is interesting that just prior to death, as I remember, he had a marked diuresis due to mercurial diuretics, and I wonder whether you would take that into consideration.

Dr. Bland: We have seen one or two things happen occasionally, especially in patients getting full doses of digitalis, if a vigorous diuresis follows the use of mercurial diuretics. Such a diuresis sometimes increases the effect of the digitalis.

We have seen patients become mildly toxic from digitalis under such circumstances. I have seen one patient recently who developed a cerebral thrombosis the night following a vigorous diuresis. Whether that was chance or was caused by a concentration of the blood, I do not know.

Clinical Diagnoses

Arteriosclerotic heart disease.
Mild congestive failure, with pulmonary congestion.
Pulmonary embolism.
Bronchiectasis?
Carcinoma of lung?

Dr. Bland's Diagnoses

Recurring pulmonary emboli.
Pulmonary infarction (multiple).
Coronary heart disease.
Phlebitis, left leg.
Bronchiectasis, mild.
Prostatic hypertrophy.

Anatomic Diagnoses

Coronary thrombosis, old and recent.
Myocardial infarction, old.
Mural thrombus, left ventricular.
Arteriosclerosis, coronary, aortic and generalized, severe.
Pulmonary infarcts, multiple.
Pericarditis, chronic, fibrous.
Rheumatic heart disease, aortic valvulitis, slight.
Infarcts of spleen.
Thrombosis of popliteal vein, left.

Pathological Discussion

Dr. Tracy B. Mallory: The post-mortem examination showed multiple pulmonary infarcts, most of them recent, although one showed evidence of organization and must have been present for a few weeks before death. The immediate mechanism of death was not a massive pulmonary embolus. The heart was very markedly hypertrophied — 575 gm. The left ventricle was much dilated as well as hypertrophied, and its entire apex consisted of a fibrous scar, overlying which was a partially organized thrombus. All the coronary arteries were markedly sclerotic, and the lumens reduced merely to slits. The main branch of the right coronary artery was completely occluded by an old organized thrombus, and the remaining portion showed a quite fresh thrombus, which I think was the immediate cause of death. There was no visible recent infarction in the heart. A very slight rheumatic deformity of the aortic valve was found, but was not, I believe, significant.

A Physician: Had there been any story of angina?

Dr. Mallory: No.

Dr. Donald S. King: Was there a chronic bronchitis?

Dr. Mallory: Not of significant grade.

Dr. Holmes: Do you think the pronounced curve in the left ventricle was due to aneurysm?

Dr. Mallory: We did not classify this as an aneurysm of the heart, although there was certainly localized dilatation.

Dr. Bland: May I ask Dr. King a question? I am uncertain what they meant by "winter bronchitis."

Dr. King: So was I. That is why I asked the question.

Dr. Mallory: I can say that there was no chronic bronchiectasis, and a little inflammatory infiltration in the bronchial walls is so usual that we do not pay much attention to it.

Dr. King: What about the spleen?

Dr. Mallory: It was somewhat enlarged. There was a localized infarct of the upper pole, definitely adherent to the diaphragm, which I think could have resulted in pressure on the fundus of the stomach.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board

Joseph Garland, M.D. — John P. Sutherland, M.D.
William B. Breed, M.D. — Stephen Rushmore, M.D.
George R. Minot, M.D. — Henry R. Viets, M.D.
Frank H. Lahey, M.D. — Robert M. Green, M.D.
Shields Warren, M.D. — Charles C. Lund, M.D.
George L. Tobey, Jr., M.D. — John F. Fulton, M.D.
C. Guy Lane, M.D. — A. Warren Stearns, M.D.
William A. Rogers, M.D. — Dwight O'Hara, M.D.
Chester S. Keefer, M.D.

Associate Editors

Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

CHEMOTHERAPY AND SEROTHERAPY OF PNEUMONIA

The season for severe respiratory infections has arrived, and the number of pneumonia cases is soon expected to reach its peak. Physicians are fortunate in having available powerful weapons with which to combat this highly fatal disease. Properly used, they are expected greatly to reduce the number of deaths from pneumonia.

The first line of therapeutic attack will be through the use of chemicals. During the present season this will mean either sulfapyridine or sulfathiazole. It has been difficult to judge which of these two drugs is superior. Each has its favorable and its unfavorable features. These have been summarized in a recent review* in the *Journal*. In general, because sulfathiazole produces nausea and vomiting less frequently and of less severity, it will probably be the drug of choice, particularly when patients are treated in the home. The mortality rate in cases treated with sulfathiazole, according to available published reports, is about the same as that in cases treated with sulfapyridine. Two points concerning the use of drugs in the treatment of pneumonia are worth repeating. The first is that sulfanilamide should not be used in the treatment of cases of acute pulmonary infection unless the infection is known to be due to a hemolytic streptococcus, and then only if sulfapyridine in adequate doses is not well tolerated. In the second place, failures from chemotherapy are to be expected, and under such conditions, changing from sulfapyridine to sulfathiazole, or vice versa, will probably not be successful except in those cases in which the change is made because of some toxic effect. Serum should be given in such cases, provided a specific type of pneumococcus is causing the infection.

*Finland, M. Treatment of pneumonia. *New Eng. J. Med.* 223:499-506, 1940.

In this issue of the *Journal* appears the reprint of a circular, issued by the Massachusetts Department of Public Health, concerning the use of sulfapyridine, sulfathiazole and specific serums in the treatment of pneumococcal pneumonias. When sulfapyridine was first introduced, many extreme views were expressed concerning the relative merits of drugs and serums. It is now recognized that both agents are effective and that they differ fundamentally in their mode of action. Almost all workers in the field of pneumonia therapy are now agreed that a certain proportion of cases of pneumococcal pneumonia fail to show adequate response to proper therapy with either sulfapyridine or sulfathiazole alone. Such failures in no wise alter the chances for success with antipneumococcus serums. Since serotherapy is highly specific, it is essential to be prepared for all contingencies by *obtaining sputum for typing and blood for culture before treatment with drugs is undertaken*. Chemotherapy need not be withheld until the results of these laboratory procedures become known, except in individual cases in which

there are definite contraindications for drug therapy. Fortunately, the latter are rare.

Early treatment with sulfapyridine or sulfathiazole offers the greatest hope for reducing the mortality from pneumonia and of bringing about rapid cures. Serum therapy is reserved for severe cases and for those in which drugs are contraindicated. In all such cases the greatest success from serotherapy is to be expected if the serum is administered early. It should also be used in all other cases due to specific types of pneumococci when, after a trial of from twenty-four to thirty-six hours, an adequately favorable response to chemotherapy has not been obtained.

The recommendations of the Massachusetts Department of Public Health in regard to the procedures to follow and the indications for drugs or for serums, or for the combination of chemotherapy and serotherapy, are a result of the summation of the experiences of a number of leading clinicians in this field. They are not absolute but are the best guide now available if one is to obtain optimum results.

The Department of Public Health is now distributing suitable containers for blood cultures. Physicians should avail themselves of this service, since pneumococcal typing is simplest and most reliable when positive blood cultures are used. Furthermore, the results of blood cultures offer the best guide for prognosis and for serum therapy. In addition, the Department of Public Health is furnishing serums for the treatment of all patients in whom positive blood cultures for specific pneumococcal types are obtained. All this should be adequate inducement to the physician for the slight additional effort required in taking such blood cultures. It should not, however, relieve him of the responsibility of seeing that sputum is properly collected and sent for typing as soon as possible after a clinical diagnosis of pneumonia is made or suspected.

CRIMINAL ASPECTS OF FAITH HEALING

To most citizens it is a novel idea that faith healing has criminal aspects, yet if one remembers the saying of a distinguished historian that "liberty, next to religion, has been the motive for good deeds and a common pretext for crime," one should not be surprised that even the practice of faith healing may on occasion violate the law of the land. As the author of an article that appears elsewhere in this issue of the *Journal* points out, the government interferes, not with religious opinions, but with the acts of individuals, it discriminates among acts expressive of religious belief, no matter how logically or illogically they may be derived from the belief, and decides that some are in violation of the law and that others are not.

It is clearly within the rights of a community to protect itself from a communicable disease in any way approved by the best scientific opinion, whether by mere restraint or isolation or by specific treatment, according to the nature of the disease and the risk of transmission from the patient to other persons. If the disease is noncommunicable and occurs in an adult of sound mind, it is generally, if not always, agreed that it is for the patient to decide whether medical advice shall be sought, and if sought, whether it shall be followed. It is in the case of noncommunicable disease occurring in the legal "infant" that controversy has been most violent. Yet here also the decisions of the courts are clear: any person who has the custody of a child is under a duty to supply the "necessaries of life, medical attention . . . included."

One point about which the various statutes differ is the pertinence of compensation in establishing violation of the law. The more general view is that the compensation is mere proof of the fact that a service has been rendered, and that other evidence is required to determine whether it was a medical or some other service for which the fee was paid.

The number of citations of court opinion raises the question whether the magnitude of the danger demands a change in the statute. The problem is not to be attacked lightly, and the situation is one that should be explored thoroughly before a specific remedy is recommended. Just what the detailed facts are, no one knows, but

it is generally true that all persons who reject medical care because of religious scruples constitute, according to their number, a very grave peril to the health of the community. There are also the possibilities of much illness and many preventable deaths, which, where "infants" are concerned, the community certainly should prevent. If it does not know, it cannot act. The situation must remain serious, because in this field no competent and critical medical opinion is available. Is the true cause of death among those who are attended by faith healers ever known?

MEDICAL EPONYM

Ghon Tubercle

In a monograph of 143 pages, Anton Ghon (1866–1936), professor of pathological anatomy at the German University in Prague, discussed *Der primäre Lungenherd bei der Tuberkulose der Kinder* [*The Primary Lung Focus in Childhood Tuberculosis*] (Berlin u. Wien, Urban u. Schwarzenberg, 1912). A portion of the translation follows:

> My investigations go back to the year 1903. They originated without any knowledge of the work of Küss. . . . The results of my studies confirm the findings of Küss and H. Albrecht. They consequently contribute nothing essentially new.
>
> We found primary lung foci in more than 75 per cent of our cases. . . . If . . . the number of primary lung infections should be reduced to even 90 per cent, they would still justify the conclusion that in the child, the primary infection of the lung is the usual form of tuberculous infection. Surely, this fact has great practical significance.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Acute Rheumatic Fever Developing During Pregnancy

Mrs. E. B., a twenty-eight-year-old para III, was admitted to the hospital on May 21, 1940, when she was five months' pregnant. She had been referred from the prenatal clinic with a history of passage of "bloody urine" for two days, with associated pain on urination, and marked weakness and night sweats since the onset of pregnancy.

The family history was noncontributory. The patient's past history included measles, whooping cough and scarlet fever. She had undergone a tonsillectomy as a child, and an appendectomy had been performed on March 25, 1940. The first pregnancy terminated in a normal delivery at eight months. The second pregnancy was complicated by albuminuria and hypertension and terminated in a breech extraction. Catamenia began at the age of thirteen, were regular with a thirty-day cycle and lasted five to six days without discomfort. The last regular period began on December 22, 1939, making the expected date of confinement, September 30, 1940.

The patient was first seen in the prenatal clinic on May 15. Physical examination at that time showed a well-developed, poorly nourished woman. The weight was 106 pounds. The heart was not enlarged; there was a harsh systolic murmur over the mitral area, transmitted to the axilla, and a soft systolic murmur was heard at the pulmonic area, not transmitted. The lungs were clear and resonant; there were no rales. The blood pressure was 120 systolic, 70 diastolic.

On admission to the hospital the patient was seen in consultation by a urologist, who advised kidney-function tests, x-ray studies and cystoscopy. A urinalysis showed a specific gravity of 1.018, a trace of albumin and a large number of red blood cells and an occasional white blood cell per high-power field. Blood examination showed a white-cell count of 10,200, a red-cell count of 3,930,000 and a hemoglobin of 74 per cent. The blood nonprotein nitrogen was 26 mg. per 100 cc., the uric acid 4.8 mg.; a phenolsulfonephthalein test showed 50 per cent excretion the first hour and 10 per cent the second. Stereograms of the chest showed increased hilar infiltration in both lungs. The heart was normal in size and position. Retrograde pyelograms of the right kidney showed a moderate degree of dilatation of the upper calyxes and ureter; there was no evidence of calculi. Bladder culture at the time of cystoscopy revealed a few gram-positive cocci; the right-kidney culture was sterile. Diagnoses of hydronephrosis and hydroureter were made.

The patient was placed on a high-vitamin, high-calorie diet, with liver and iron therapy. On May 27, one week after admission, the patient's temperature rose to 101°F., and she complained of a sore throat. Examination revealed uniform redness of the postpharyngeal wall. On the following day she complained of tenderness and stiffness of the left knee and ankle. On examination

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

there were redness, swelling, tenderness and limitation of motion of the left knee and ankle. A medical consultation was held, and the consultant's impression was that the patient had acute rheumatic fever with early endocarditis. She was placed on salicylate therapy. Repeated urinalyses continued to show a slight trace of albumin and a large number of white blood cells in the sediment. On May 29 the blood white-cell count was 9100; on June 7, 14,100; on June 20, 11,800; on July 3, 14,300; and on July 26, 7200.

The patient also complained of recurring bouts of uterine contractions. These were controlled with medication. The uterus had increased to a size consistent with the date of the last menstrual period; the fetal heart tones were of good quality.

She continued to run a temperature ranging from 98 to 101°F. Two weeks after the onset of infection the left wrist and elbow became similarly involved. On July 20 the temperature dropped to normal, and remained at that level until delivery. The acute inflammation of the joints subsided shortly thereafter, leaving only a stiffness of the left ankle joint.

During hospitalization there were no signs or symptoms of cardiac decompensation. The blood pressure was never higher than 120 systolic, 70 diastolic.

The patient started in active labor spontaneously on September 12 at 10 a.m. Analgesia consisted of 6 gr. of Nembutal. At 1:30 p.m., under light ether anesthesia, she was delivered of a living male child, weighing 6 pounds, 10 ounces. The puerperium was uneventful, and the patient was discharged on October 5.

Examination of the heart at the time of discharge showed no enlargement by percussion or x-ray. There was no rub. The rhythm was regular, the rate 76. The sounds were of good quality. There was a soft systolic murmur at the apex, not transmitted. There were no other murmurs. The blood pressure was 110 systolic, 70 diastolic.

Comment. This is a very interesting case of acute rheumatic fever that developed during pregnancy. The treatment was extremely conservative, the patient remaining in the hospital from the onset until after delivery, which was normal. The evidence of heart disease was minimal, and there were no periods of decompensation. At last note the patient's heart was well compensated and showed no evidence of serious damage.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning February 9:

MIDDLESEX EAST

Tuesday, February 11, at 4:15 p.m., at the Melrose Hospital, Melrose. Technic and Treatment of Primary, Secondary and Tertiary Syphilis. Instructor: William P. Boardman. Walter H. Flanders, *Chairman.*

MIDDLESEX SOUTH

Tuesday, February 11, at 4:00 p.m., at the Cambridge Hospital, Mt. Auburn Street, Cambridge. Chemotherapy in the Treatment of Gonococcal Infection. Instructor: Oscar F. Cox. Dudley Merrill, *Chairman.*

NORFOLK

Thursday, February 13, at 8:30 p.m., at the Norwood Hospital, Norwood. Recent Advances in Medical Therapeutics. Instructor: Charles L. Short. Hugo B. C. Riemer, *Chairman.*

NORFOLK SOUTH

Monday, February 10, at 8:30 p.m., at the Quincy City Hospital, Quincy. Pediatric Case Discussions. Instructor: James M. Baty. David L. Belding, *Chairman.*

SUFFOLK

Thursday, February 13, at 4:30 p.m., in John Ware Hall, Boston Medical Library. Acute Abdominal Pain. Instructor: Stanley J. G. Nowak. Reginald Fitz, *Chairman.*

DEATHS

BUCKLEY — James T. Buckley, M.D., of Worcester, died January 24. He was in his sixty-fifth year.

Dr. Buckley attended Williams College and received his degree from the Baltimore Medical College in 1902. He had been practicing in Worcester for over twenty years, and prior to that had practiced in Marlboro for about fifteen years.

He was a former member of the Massachusetts Medical Society and the American Medical Association.

His widow, two daughters and two sons survive him.

WEEKS — Joshua F. Weeks, M.D., of New Bedford, died January 12. He was in his seventy-fifth year.

Born in Dartmouth, he attended the University of the Green Mountains, Burlington, Vermont, and received his degree from the University of Vermont College of Medicine in 1890. He settled in New Bedford and began practice.

Dr. Weeks was a member of the Massachusetts Medical Society, the American Medical Association and the New Bedford Medical Society.

Two children survive him.

CORRESPONDENCE

TREATMENT OF PNEUMOCOCCAL PNEUMONIA

To the Editor: The Massachusetts Department of Public Health has recently revised its circular on the use of the specific drugs in the treatment of pneumonia. With this exception the pneumonia program of the department is the same as that of last year. The program includes:

The provision of concentrated therapeutic (horse) serums for Types 1, 2, 5, 7 and 8, obtainable for the treatment of patients with infections due to one of these types, as determined by an approved typing laboratory.

The provision of concentrated therapeutic (rabbit) serums for Types 4, 9, 14 and 18 on the basis indicated above.

The provision of concentrated therapeutic (rabbit) serums of all other types for patients with *bacteremia, meningitis* or *peritonitis* due to one of these types, the determination of which has been made by an approved typing laboratory.

A circular describing the use of sulfapyridine and sulfathiazole in treatment of pneumococcal pneumonia.

Revised case-report forms, supplied by the department, which must be completed and returned to the department for all serum-treated cases.

Receipt forms which must be signed by the physician receiving the serum and by the issuing agency.

The distribution of therapeutic horse serums will be continued as in previous years through typing laboratories. Therapeutic rabbit serums for Types 4, 9, 14 and 18 will be available through the five typing laboratories from which they were supplied last season. All other therapeutic rabbit serums will be available from only two points — the Bacteriological Laboratory at the State House, Boston, and the Westfield State Sanatorium at Westfield.

The rabbit serums are being purchased, and the amount of money available for this purpose may not suffice for all demands. Therefore, the continuation of this service will depend greatly on the conservation of funds effected through the prompt return of unused serum.

Copies of the new drug circular and the list of approved typing laboratories and serum stations are being mailed to all physicians in the State and are also available at the approved typing laboratories. Additional copies of the circular and the list of the laboratories at which the various serums may be obtained will be furnished by the department on request. They are reproduced below.

PAUL J. JAKMAUH, M.D.,
Commissioner of Public Health.

State House,
Boston.

* * *

THE SULFONAMIDE DERIVATIVES, SULFAPYRIDINE AND SULFATHIAZOLE, IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

These drugs and antipneumococcic serum are of definite value in treating pneumococcal pneumonias. Sulfapyridine and sulfathiazole appear to be about equally effective and are superior to sulfanilamide. Sulfapyridine is superior to sulfathiazole in the treatment of pneumococcal meningitis.

I. *Before starting treatment* with drug or serum:

1. Obtain sputum for typing and blood for culture.
2. Make complete blood counts, including red and white cells, differential and hemoglobin determination.
3. Make complete urine examination; and, if indicated, blood nonprotein nitrogen determination.

(2 and 3, above, should be done daily while patient is receiving sulfapyridine or sulfathiazole in full doses, or if abnormalities are encountered; and every 2 to 3 days during entire period of drug adminstration.)

II. *General Considerations.* Because the drugs and the serum differ in their mode of action, neither is a complete substitute for the other. Sulfapyridine and sulfathiazole inhibit the multiplication of the pneumococcus, whereas specific serum furnishes additional antibodies which may be necessary for the destruction of the organisms. By combining drug and serum less of each may be needed than either would require alone. Unless one or the other is contraindicated, serum is recommended as a supplement to either sulfapyridine or sulfathiazole in the following situations:

1. Treatment is begun after the third day of the disease.
2. Patient is over 50 years old.
3. Patient is pregnant or in first week of puerperium.
4. Pneumococcus bacteremia is known to be present.
5. There is involvement of more than one lobe.
6. There is no obvious improvement within 18–24 hours after the initial dose of sulfapyridine or sulfathiazole; serum therapy may be delayed to 24–36 hours after the initial dose of the drug in the absence of 1–5 above.

III. *Contraindications to the Use of Sulfapyridine or Sulfathiazole.* Only under the most exceptional circumstances should sulfapyridine or sulfathiazole be given in the presence of either of the following conditions:

1. History of previous toxic reactions (anemia, agranulocytopenia, anuria, hematuria or hepatitis) to any of the *sulfonamide derivatives.*
2. Hemolytic anemia or granulocytopenia from any cause.

A difference of opinion exists as to the importance of previous drug rash, impaired kidney function or jaundice as a contraindication to sulfapyridine or sulfathiazole therapy; therefore the desirability of treating patients with these conditions is a matter of judgment. Great care must be exercised under these conditions, and the drug stopped at the first evidence that the functions are further impaired or if the drug rash recurs.

If a drug is to be given to postoperative patients, sulfathiazole is less likely than sulfapyridine to cause vomiting.

IV. *Dosage and Procedure of Treatment.* The rate and degree of absorption and excretion of sulfapyridine and sulfathiazole are variable, hence there can be no hard and fast rule of dosage. When oral administration is interfered with by vomiting or when it fails to give an adequate blood drug concentration,

Laboratories for Pneumococcus Typing and Serum Distribution.

City or Town	Hospital or Other Agency	Specimens Typed for Types 1, 2, 3, 4, 5, 7, 8, 9, 14 and 18 (plus Pools A–F), Except as Indicated	Type of Therapeutic Serum for Distribution	Specimens Accepted†
Amesbury	*Amesbury Hospital		None	A
Arlington	*Symmes Arlington Hospital		None	A
Ayer	Community Memorial Hospital	1–33	1	A
Beverly	Beverly Hospital	1–33	1, 2, 5, 7, 8	A
Boston	Antitoxin and Vaccine Laboratory	No typing	1, 2, 5, 7, 8	No typing
	Beth Israel Hospital		1	A
	Boston City Hospital	1–33	None	A
	*Carney Hospital		1	H
	Children's Hospital	1–33	None	S
	Faulkner Hospital	1–33	1, 2, 5, 7, 8	A
	*Long Island Hospital		None	H
	*Massachusetts General Hospital	1–33	1	S
	*Massachusetts Memorial Hospitals	1–33	None	A
	*New England Deaconess Hospital		None	A
	*New England Hospital for Women and Children	1–33	None	S
	Peter Bent Brigham Hospital	1–33	1, 2, 5, 7, 8	H
	STATE BACTERIOLOGICAL LABORATORY	1–33	All types	A
	*St. Elizabeth's Hospital	1–33	1	A
Brockton	Board of Health Laboratory	1–33	None	A
	Brockton Hospital	1–33	1, 2, 5, 7, 8	A
Cambridge	*Cambridge City Hospital		1	M
	Cambridge Hospital	1–33	1	A
Chelsea	Chelsea Memorial Hospital		1	H
Clinton	Clinton Hospital		1	A
Everett	*Whidden Memorial Hospital	1–33	1	A
Fall River	Fall River General Hospital		1	A
	*St. Anne's Hospital		1	A
	*Truesdale Hospital	1–33	1	A
	Union Hospital	1–33	1	A
Fitchburg	Burbank Hospital	1–33	1, 2, 5, 7, 8	A
Foxboro	Foxboro State Hospital		None	H
Framingham	*Framingham Union Hospital	1–33	1, 2, 5, 7, 8	A
Gardner	Henry Heywood Memorial Hospital		1	A
Gloucester	*Addison Gilbert Hospital	1–33	1	S
Great Barrington	*Fairview Hospital		1	A
Greenfield	Franklin County Hospital	1–33	1, 2, 5, 7, 8	A
Haverhill	Hale Hospital	1–33	1, 2, 4, 5, 7, 8, 9, 14, 18	A
Holyoke	Holyoke Hospital	1–33	1	A
	Providence Hospital	1–33	1, 2, 4, 5, 7, 8, 9, 14, 18	A
Hyannis	Cape Cod Hospital	1–33	1, 2, 5, 7, 8	A
Ipswich	Cable Memorial Hospital	1–33	None	A
Lawrence	Lawrence General Hospital		1	A
Leominster	*Leominster Hospital		1	M
Lowell	Lowell General Hospital		1	A
	St. John's Hospital	1–33	1	A
	St. Joseph's Hospital	1–33	1, 2, 5, 7, 8	A
Lynn	*Board of Health		None	M
	*Lynn Hospital	1–33	1, 2, 5, 7, 8	A
	*Union Hospital		1	A
Malden	Malden Hospital	1–33	1	A
Marlborough	*Marlborough Hospital		1	S
Melrose	Melrose Hospital		None	A
Middleborough	St. Luke's Hospital		1	A
Milford	Milford Hospital		1	A
Montague City	Farren Memorial Hospital	1–33	None	A
Nantucket	*Nantucket Cottage Hospital	1–33	1	A
Natick	*Leonard Morse Hospital		1	S
New Bedford	St. Luke's Hospital	1–33	1, 2, 4, 5, 7, 8, 9, 14, 18	A
Newburyport	*Anna Jaques Hospital		1	S
Newton	Newton Hospital	1–33	1	A
Norfolk	*Pondville State Hospital	1–33	1, 2, 5, 7, 8	A
North Adams	North Adams Hospital		1	A
Northampton	Cooley Dickinson Hospital	1–33	1	A
	*Northampton State Hospital		None	H
Norwood	*Norwood Hospital		1	A
Palmer	*Wing Memorial Hospital		None	A
Peabody	*Josiah B. Thomas Hospital		None	A
Pittsfield	House of Mercy Hospital	1–33	1, 2, 5, 7, 8	A
	*St. Luke's Hospital	1–33	1	A
Plymouth	*Jordan Hospital		1	A
Pocasset	*Barnstable County Sanatorium	1–33	1	A
Quincy	Quincy City Hospital	1–33	1, 2, 5, 7, 8	A
Salem	*Salem Hospital	1–33	1	A
Somerville	*Somerville Hospital		1	A
Southbridge	*Harrington Memorial Hospital		1	A
Springfield	Mercy Hospital	1–33	1, 2, 5, 7, 8	A
	Springfield Hospital	1–33	1	A
	Wesson Memorial Hospital	1–33	1	A
Taunton	Morton Hospital	1–33	1	A
	State Hospital		None	H
Tewksbury	State Infirmary	1–33	1	H
Waltham	*Metropolitan State Hospital		None	H
	*Waltham Hospital	1–33	1	A
Ware	*Mary Lane Hospital		1	A
Webster	*Webster District Hospital		1	A
Westfield	*Noble Hospital	1–33	None	A
	*WESTFIELD STATE SANATORIUM	No typing	All types	No typing
Weymouth	Weymouth Hospital		None	A
Winthrop	Winthrop Community Hospital		None	A
Worcester	Memorial Hospital	1–33	1	A
	St. Vincent Hospital	1–33	1	A
	Worcester City Hospital	1–33	1, 2, 4, 5, 7, 8, 9, 14, 18	A
	*Worcester Hahnemann Hospital		1	A
	Worcester State Hospital		None	H

*Approval pending; application made and evaluation of performance is in progress.

†Specimens for typing accepted from: S = staff members and hospital cases only; A = any physician; H = hospital cases only; M = any physician in municipality.

Typings are done without charge at the State Bacteriological Laboratory, Boston. All other laboratories, except those maintained by municipalities, charge fees for typing. Special arrangements can be made for typings done on persons unable to pay when treated in the home.

resort may be had to the intravenous use of sodium sulfapyridine. Because of the danger of venous thrombosis and perivascular necrosis, the use of sodium sulfapyridine should be restricted to such cases. For details of its use, reference should be made to the manufacturers' circulars.

In general the following procedure for oral administration is at present recommended:

1. Dosage. (The drug is given orally and on schedule; the patient should be awakened if necessary to give drug.)
   a. Adults: 2 gm., followed in 4 hours with 1 or 2 gm., then 1 gm. every 4 hours until temperature, pulse and respiration are essentially normal for 48 hours; then 1 gm. every 6 hours for 2 to 3 days. From the standpoint of safety the drug should not be continued for longer than 96 hours unless daily blood drug-level determinations are being made.
   b. Infants and children: initial dose 0.25 gm. per 10 lb. body weight and maintenance dose 0.75 gm. per 10 lb. body weight per 24 hours administered in divided doses at 4 to 6-hour intervals.
   c. The giving of the drug in milk, fruit juice, gruel or applesauce may be helpful. For nausea, small doses of one of the milder sedatives or carminatives may be tried. It is well to remember that, with vomiting, there may be some loss of fluids and chlorides, as well as a loss of the drug, and infusions of saline subcutaneously or intravenously may be necessary to replace these losses.
2. Relapse or extension may occur if:
   a. The drug is discontinued too soon after a therapeutic response has been obtained, particularly in cases treated early in the course of the illness; or
   b. The pneumococcus causing the infection becomes resistant to the drug (sulfapyridine or sulfathiazole fast); if this occurs, further treatment with the drugs is of no avail and serum therapy is indicated.
3. The action of the drug may mask the symptoms of empyema or other surgical conditions, but does not lessen the need for surgical action in such conditions.
4. Blood drug-level estimations should be made after 12 to 18 hours of treatment and every 1 to 2 days thereafter; a level of 4 to 6 mg. of free drug per 100 cc. of blood is usually considered adequate, and a level of 15 mg. is probably the upper limit of safety.

V. *Reactions from Sulfapyridine or Sulfathiazole.*

1. Those reactions which require stopping the drug and, in some cases, active therapeutic measures are:
   a. Blood changes, which may include hemolytic (or other severe) anemia and granulocytopenia;
   b. Effects on the urinary system, which may include gross hematuria, ureteral pain, urinary obstruction, nitrogen retention and nephritic edema;
   c. Toxic hepatitis, evidenced by jaundice.
2. Reactions which may require stopping the drug and institution of appropriate therapy are:
   a. Severe and persistent nausea and vomiting, particularly when associated with postoperative cases, loss of chlorides, etc. (See IV 1 *c.*);
   b. Drug fever, drug rashes; and
   c. Marked central-nervous-system disorders, including vertigo, headache and mental depression or excitement.

Reactions may be detected early or sometimes avoided if the precautions outlined in Sections 1, 2 and 3 and Section IV 4 are followed.

These recommendations have been approved by the Pneumonia Advisory Committee.

REPORT OF MEETING

WILLIAM HARVEY MEDICAL SOCIETY

A regular meeting of the William Harvey Medical Society of Tufts College Medical School was held at the Beth Israel Hospital on November 8, 1940, with Dr. William Dameshek presiding. Dr. Maxwell M. Wintrobe of Johns Hopkins Medical School spoke on "Experimental Studies on Pernicious Anemia, with Particular Reference to the Central-Nervous-System Manifestations."

In introduction the speaker reviewed the outstanding clinical, laboratory and historical data relative to pernicious anemia. The chief difficulty in the experimental production of the syndrome has been the inability consistently to produce in lower animals a picture similar to that of human beings. It has been found nearly impossible to devise an adequate diet lacking in extrinsic factor, and intrinsic factor has been demonstrated to exist in other parts of the gastrointestinal tract than the stomach.

Dr. Wintrobe's attack on the problem originated in the observation that the number of erythrocytes increases and the size decreases as one ascends the phylogenetic scale, as well as the embryologic scale, of mammals. Nucleation of erythrocytes occurs in the early mammalian fetus as well as in the phylogenetic scale below man. These features are similar to the changes that occur in pernicious anemia as the anemia is relieved by therapy. It was also found that fetal liver extracts were not potent in curing pernicious anemia. Because of these analogies with the condition found in pernicious anemia during relapse, it was decided to attempt to produce pernicious anemia in very young animals. Newborn pigs were used as the experimental animal because of their size and because this animal is a source of commercial liver extract.

Initially it was found that the basic experimental diets were deficient in the water-soluble vitamins, and yeast was consequently added. But this was found to contain blood-regenerating substances, and synthetic vitamin B products were therefore substituted when they became available. In a large group of pigs on this inadequate diet a few animals developed a macrocytic anemia; but all the animals developed marked ataxia. Pathologically the findings in the central nervous system resembled those of pernicious anemia except in lack of degeneration in the lateral funiculi.

A summary of the experiments of Dr. Wintrobe revealed that animals on inadequate yeast intake were not protected from the development of ataxia by thiamin, riboflavin or nicotinic acid, singly or in any combination; yeast, even in huge doses, did not protect all the animals, although those which eventually became ataxic were carried on for long periods without ataxia; control experiments ruled out inanition as the cause of the nervous system changes; addition of whole liver completely protected the animals; wheat-germ oil gave no protection. The effect of various liver fractions is now being investigated, and the indications are that the Cohn fraction is protective, whereas the Whipple fraction is not; recent observations indicate that protection is given by vitamin B_1, choline and pantothenic acid in combination, or possibly by one of these alone.

The relation of these experiments to pernicious anemia is still indirect and uncertain, Dr. Wintrobe stated. However, it has been found that liver extracts made from ataxic pigs are ineffective in treating pernicious anemia, in contrast to those from pigs on adequate diets including liver or potent yeast. The puzzling question is, If the pigs' livers are lacking in the antipernicious anemia factor, why do these animals not develop macrocytic anemia?

Dr. Wintrobe suggested that pernicious anemia may be a syndrome resulting from a deficiency of several factors, such as that found in pellagra. If this is so, the distribution of the factors in usual diets would explain why one person develops hematologic manifestations, another neurogenic and another gastrointestinal. This is borne out clinically by the cases of severe anemia without symptoms in the central nervous system, and those with severe combined system disease and minimal macrocytic anemia.

During the discussion Dr. Wintrobe answered questions posed by the audience. The amount of liver extract employed in his experiments was comparable to the human therapeutic dosage. Yeast is variable in its content of antianemic factors, depending on the mode of manufacture. The speaker cited the results of Strauss and Castle in obtaining a reticulocyte response by feeding yeast with gastric juice. Dr. Wintrobe obtained similar results with large doses of yeast alone in those patients who were able to respond to oral therapy. The presence of achlorhydria was variable in controls and experimental animals. It appeared and disappeared from time to time and therefore was not considered significant. No consistent buccal mucosal changes were noted.

NOTICES

HARVARD MEDICAL SOCIETY

There will be a meeting of the Harvard Medical Society on Tuesday, February 11, in the amphitheater of the Peter Bent Brigham Hospital at 8:15 p.m. Dr. Soma Weiss will preside.

PROGRAM

Presentation of cases.
Pneumonia. Dr. Maxwell Finland.

Beginning with the February 11 meeting, the Harvard Medical Society will meet on the second Tuesday of each month rather than bimonthly as in the past.

SOUTH END MEDICAL ASSOCIATION

There will be a meeting of the South End Medical Club at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 18, at 12 m. Dr. Frank R. Ober will speak on "Chronic Arthritis."

Physicians are cordially invited to attend.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, formerly concertmaster of the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

MASSACHUSETTS MEMORIAL HOSPITALS

There will be a research conference at the Robert Dawson Evans Memorial, 78 East Concord Street, Boston, on Wednesday, February 12, at 5 p.m. Dr. William E. Long will speak on "Mapharsen in the Treatment of Forty Patients Following Arsphenamine Dermatitis."

Physicians and medical students are invited to attend.

SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, Boston, on Thursday, May 1, at 4:00 p.m.

Candidates should make personal application to the secretary and present their medical diplomas at least six weeks before examination (if graduates of foreign medical schools or schools not on the list recognized by the Council, at least eight weeks before).

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM, FEBRUARY

Tuesday, February 11 — Blood Transfusion: Past, present and future. Dr. H. G. Brugsch.

Wednesday, February 12 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, February 13 — Artificial Pneumoperitoneum. Dr. O. B. Lewis.

Friday, February 14 — Certain Aspects of Leukemia. Dr. Henry Jackson, Jr.

Saturday, February 15 — Hospital case presentation. Dr. S. J. Thannhauser.

Tuesday, February 18 — The Psychosomatic Problem: Its significance for the physician. Dr. Kurt Goldstein.

Wednesday, February 19 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, February 20 — The Perennial Tonsil Problem. Dr. W. A. MacColl.

Friday, February 21 — Some Characteristics of Experimental Deficiency Diseases. Dr. O. A. Bessey.

Tuesday, February 25 — X-ray demonstration. Dr. Alice Ettinger.

Wednesday, February 26 — Hospital case presentation. Dr. S. J. Thannhauser.

Thursday, February 27 — Advances in chemotherapy. Dr. C. A. Janeway.

Friday, February 28 — Gastrointestinal clinic. Dr. K. S. Andrews.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held at the Beth Israel Hospital on Monday, February 24, at 8:15 p.m.

PROGRAM

Demonstration of a Method Useful in Teaching Electrocardiograph. Dr. J. E. F. Riseman.

The Incidence and Location of Occlusions in the Various Coronary Arteries. Dr. M. J. Schlesinger.

Postoperative Thrombophlebitis: Factors impeding circulation and changes in venous pressure during abdominal operations. Drs. David Davis and Samuel Gilman.

Cardiovascular Dynamics in Patients with Superior Caval Obstruction. Dr. M. D. Altschule.

An Unusual Problem in Differential Diagnosis: With x-ray demonstration. Drs. Karl Presser and S. A. Robins.

Further Studies in the Appraisal of Therapeutic Measures for Angina Pectoris. Dr. A. S. Freedberg.

The Relation Between Electrocardiographic Changes and Coronary Artery Pathology. Drs. P. M. Zoll and Erwin Spiegl.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The next regular meeting of the New England Dermatological Society, which was scheduled for February 12 at the Massachusetts General Hospital, *has been canceled* because of the proximity of the Atlantic Dermatologic Conference to be held on March 22.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

There will be a meeting of the New England Society of Physical Medicine at the Hotel Kenmore, Boston, on Wednesday, February 19, at 8:00 p.m. A business meeting at 6:00 p.m. will be followed by an informal dinner in the Empire Room at 6:30 p.m.

PROGRAM

Medical Preparedness. Dr. Walter G. Phippen, president, Massachusetts Medical Society.

All members of the medical profession are cordially invited to attend.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire board from Wednesday, May 28, to Monday, June 2, inclusive, prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the secretary's office not later than March 1.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for re-examination in Part II must make written application to the secretary's office before April 15, 1941.

In accordance with the previously announced plans of the board, the examinations to be given for the board's fiscal year 1941–42 (ending with the Part II examination in June, 1942) will be the last for candidates under Group A and B classifications. Applications must be in the secretary's office at least ninety days in advance of the announced examination dates, which dates are published in the various medical journals. Following the close of the final date for receipt of Group B applications (October, 1941) and Group A applications (March, 1942) all candidates will be considered in one classification by the board, thus doing away with the junior and senior groups for examination, and all candidates will be required to take the Part I examination (written paper and submission of case histories) as well as the Part II examination (oral and pathological).

Military service will not affect the eligibility of any candidate so far as the board requirements regarding limitation of practice are concerned. Military service will under no circumstances be considered as an infringement of any regulations outlined in this board's booklet.

The board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has been inaugurated by the board this year. The secretary will be glad to furnish these forms on request, together with information regarding board requirements. Address: Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, FEBRUARY 9

SUNDAY, FEBRUARY 9

†4 p.m. Medical Problems Presented by Selective Service. Dr. Frederick F. Russell. Free public lecture. Harvard Medical School, Building D.

†4 p.m. Immunization Against Contagious Diseases. Dr. Charles F. Walcott. Cambridge Hospital, Margaret Jewett Hall.

MONDAY, FEBRUARY 10

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

TUESDAY, FEBRUARY 11

*9–10 a.m. Blood Transfusion: Past, present and future. Dr. H. G. Brugsch. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

8 p.m. Boston City Hospital, Dowling Surgical Building. New England Society of Anesthesiology.

*7:45 p.m. The Present Status of Physiotherapy in the Treatment of Chronic Arthritis. Dr. Arthur L. Watkins. Robert Breck Brigham Hospital.

8:15 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.

WEDNESDAY, FEBRUARY 12

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

*2–4 p.m. Obesity. Drs. J. C. Aub and F. C. Newton. Peter Bent Brigham Hospital.

*5 p.m. Mapharsen in the Treatment of Forty Patients Following Arsphenamine Dermatitis. Dr. William E. Long. Massachusetts Memorial Hospitals.

THURSDAY, FEBRUARY 13

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9–10 a.m. Artificial Pneumoperitoneum. Dr. O. B. Lewis. Joseph H. Pratt Diagnostic Hospital.

*8:15 p.m. Alcoholism. Dr. Merrill Moore. United States Naval Hospital, Chelsea.

FRIDAY, FEBRUARY 14

*9–10 a.m. Certain Aspects of Leukemia. Dr. Henry Jackson, Jr. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, FEBRUARY 15

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.
†Open to the public.

FEBRUARY 11–28 — Joseph H. Pratt Diagnostic Hospital, medical conference program. Page 261.

FEBRUARY 13 — Pentucket Association of Physicians. Page 263, issue of August 15.

FEBRUARY 18 — South End Medical Club. Page 261.

FEBRUARY 19 — Boston Society of Biologists. Page 218, issue of January 30.

FEBRUARY 19 — New England Society of Physical Medicine. Page 262.

FEBRUARY 20–22 — American Orthopsychiatric Association, Inc. Page 999, issue of December 12.

FEBRUARY 24 — New England Heart Association. Page 262.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

MARCH 12–14 — New England Hospital Assembly. Hotel Statler, Boston.

MARCH 21–22 — New York University College of Medicine, Alumni Day. Page 135, issue of January 16.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

MAY 21, 22 — Massachusetts Medical Society, Boston.

MAY 28–JUNE 2 — American Board of Obstetrics and Gynecology. Page 262.

JUNE 2–6 — American Medical Association. Cleveland, Ohio.

OCTOBER 14–17 — American Public Health Association. Page 135, issue of January 16.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

MARCH 5 — X-ray in Heart Disease. Dr. Merrill C. Sosman. Essex Sanatorium, Middleton.

APRIL 2 — Pediatric Problems in General Practice. Dr. Joseph Garland. Addison Gilbert Hospital, Gloucester.

MAY 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

MARCH 11.

MAY 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

NORFOLK

FEBRUARY 25 — Medicolegal meeting. 8:30 p.m. Hotel Puritan, Boston.

MARCH 25 — To be announced.

MAY 8 — Censors' meeting. Hotel Puritan.

SUFFOLK

APRIL 30 — Page 604, issue of October 10.

MAY 1 — Censors' meeting. Page 261.

WORCESTER

FEBRUARY 12 — Worcester State Hospital, Worcester.

MARCH 12 — Memorial Hospital, Worcester.

APRIL 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Photodynamic Action and Diseases Caused by Light. By Harold Francis Blum, Ph.D. The Washington Biophysical Institute. 8°, cloth, 309 pp., with 25 tables and 50 illustrations. New York: Reinhold Publishing Corporation, 1941. $6.00.

The Role of the Liver in Surgery. By Frederick Fitzherbert Boyce, M.D., visiting surgeon, Charity Hospital of Louisiana at New Orleans, French Hospital, Mercy Hospital, Hotel Dieu, Southern Baptist Hospital and Touro Infirmary. 4°, cloth, 365 pp., with 44 illustrations. Springfield, Illinois: Charles C Thomas, 1941. $5.00.

A History of Medicine. By Arturo Castiglioni, M.D., research associate in the history of medicine, Yale University. Translated from the Italian and edited by E. B. Krumbhaar, M.D., Ph.D., honorary president of the American Association of the History of Medicine. 8°, cloth, 1013 pp., with 443 illustrations. New York: Alfred A. Knopf, 1941. $8.50.

What Are the Vitamins? By Walter H. Eddy, Ph.D., director of *Good Housekeeping* Bureau, and professor of physiological chemistry, Teachers College, Columbia University. 8°, cloth, 247 pp. New York: Reinhold Publishing Corporation, 1941. $2.50.

Modern Drug Encyclopedia and Therapeutic Guide. By Jacob Gutman, M.D., Phar.D., director, Brooklyn Diagnostic Institute, and consulting physician, Manhattan General Hospital, New York City, and the Riverdale, Shore Road, Williamsburg Maternity and Borough Park General hospitals, Brooklyn. Second edition. 8°, cloth, 1644 pp. New York: New Modern Drugs, 1941. $7.00.

Bacteriology in Neuropsychiatry: A survey of investigations concerned with the specific role of infections and immune processes. By Nicholas Kopeloff, Ph.D., research bacteriologist, New York State Psychiatric Institute and Hospital, New York City. 8°, cloth, 316 pp., with 11 tables. Springfield, Illinois: Charles C Thomas, 1941. $4.50.

Food, Teeth and Larceny. By Charles A. Levinson, D.M.D. 8°, cloth, 232 pp. New York: Greenberg, 1940. $3.00.

A Textbook of Clinical Neurology. By J. M. Nielsen, M.D., associate clinical professor of medicine (neurology), University of Southern California, senior attending physician (neurology), Los Angeles County General Hospital, and attending neurologist, Hospital of the Good Samaritan, Los Angeles. 4°, cloth, 672 pp., with 179 illustrations. New York: Paul B. Hoeber, Incorporated, 1941. $6.50.

The Extra-Ocular Muscles: A clinical study of normal and abnormal ocular motility. By Luther C. Peter, M.D., Sc.D., LL.D., professor emeritus of diseases of the eye, Graduate School of Medicine, University of Pennsylvania, member of consulting staff, Graduate Hospital, University of Pennsylvania, and consulting ophthalmologist, Rush Hospital for Consumption and Allied Diseases, Friends' Hospital for Nervous and Mental Diseases and Roxborough Memorial Hospital. Third edition, thoroughly revised. 8°, cloth, 368 pp., with 147 illustrations and 5 colored plates. Philadelphia: Lea and Febiger, 1941. $4.50.

Diseases of the Digestive System. Edited by Sidney A. Portis, M.D., associate clinical professor of medicine, Rush Medical College, University of Chicago, attending physician, Michael Reese Hospital, and consulting physician, Cook County Hospital, Chicago. 8°, cloth, 952 pp., with

176 illustrations and 37 tables. Philadelphia: Lea and Febiger, 1941. $10.00.

Medicine and Health in New Zealand: A retrospect and a prospect. By Douglas Robb, M.D., Ch.M., F.R.C.S. (Eng.). 8°, cloth, 146 pp. Auckland, New Zealand: Whitcombe and Tombs, Limited, 1940. 8/6.

Studies on the Human Thyroid in Iceland. By Julius Sigurjónsson. 8°, paper, 130 pp., with 21 tables and 10 figures. Reykjavik: Prentsmidjan Edda H. F., 1940. 6s. Obtainable from H. K. Lewis and Company, Limited, London.

Plague on Us. By Geddes Smith, M.D. 8°, 365 pp., with 24 illustrations. New York: The Commonwealth Fund, 1941. $3.00.

Strange Malady: The story of allergy. By Warren T. Vaughan, M.D. 8°, cloth, 268 pp., with 23 illustrations. New York: Doubleday, Doran and Company, Incorporated, 1941. $3.00.

Radiologic Physics. By Charles Weyl, B.S., M.S.; S. Reid Warren, Jr., B.S., Sc.D.; and Dallett B. O'Neill — Moore School X-Ray Laboratory, Moore School of Electric Engineering, University of Pennsylvania. With a foreword by Eugene P. Pendergrass, M.D., director of the Department of Radiology, University of Pennsylvania. 8°, cloth, 460 pp., with 166 illustrations and 33 tables. Springfield, Illinois: Charles C Thomas, 1941. $5.50.

The Medical Reports of John Y. Bassett, M.D. The Alabama Student. With an introduction by Daniel C. Elkin, M.D., Joseph B. Whitehead Professor of Surgery, Emory University. 12°, cloth, 62 pp., illustrated. Springfield, Illinois: Charles C Thomas, 1940. $1.50.

A Textbook of Clinical Pathology. Edited by Roy R. Kracke, M.D., professor of pathology and bacteriology, Emory University; and Francis P. Parker, M.D., assistant professor of pathology and bacteriology, Emory University. Second edition. 8°, cloth, 780 pp., with 223 illustrations, 26 tables and 34 colored plates. Baltimore: Williams and Wilkins Company, 1940. $6.00.

BOOK REVIEWS

Sex in Marriage. By Ernest R. Groves, B.D., and Gladys Hoagland Groves. 12°, cloth, 250 pp. New York: Emerson Books, Inc. $2.00.

With characteristic frankness and in a pleasing style the Groveses have made an addition to what is now becoming a small library by these authors on the subject of family adjustments. The reader who is acquainted with their previous writings will find nothing particularly new in attitude or style of presentation. Those who have read a number of the present-day frank studies in sex will find in this book little new information and nothing that tends to stimulate erotic interest. It does not deal with descriptions of deviations so much sought after by the curious minded. It is a book that could be put into the library of any home and should be available to the adolescent and young adult when parents desire to create a wholesome and factual attitude toward sex.

The reviewer does not wish to create the impression that this is a dull book; it is far from that. There are ten chapters. The first deals with sex in its relation to happiness and makes a strong plea for an understanding of the rightful place of sex in life. It upholds the place of sex curiosity in the lives of children and takes to task those who interpret such curiosity as unwholesome and offensive.

Emphasis is next placed on the importance of considering one's own background in making marriage adjustments, and this is followed by an interesting and practical statement regarding emotional problems arising from courtship.

The chapter on "Sex Equipment" is good, but its value would have been increased tenfold by the use of descriptive charts. To the visual minded nothing can take the place of pictures in the comprehension of physical structure and functioning.

In the chapter "The Beginnings of Marriage" there is a weakness that probably lies in the authors' withdrawal from any consideration of emotional deviations. It is too big a problem to discuss in a review, and if not fully considered, analysis might be unfair to the authors. The reviewer is constrained, however, to make the point that there is an error in the assumption that "cave-man tactics" are always disagreeable to the woman. There is a failure here to recognize that there are many women whose masochistic response to this somewhat sadistic approach is altogether satisfying. It seems a mistake to assume that such women are not normal. There is too great a tendency on the part of all authors to assume that those things with which they disagree and toward which they have a personal distaste are not normal, and that normality can be measured only by their own standards.

The subsequent chapters are interesting and instructive. On the whole it is a book that one need have no hesitancy in recommending to those who seek enlightenment on this subject.

Physical Diagnosis. By Ralph H. Major, M.D. Second edition, revised. 8°, cloth, 464 pp., with 437 illustrations. Philadelphia and London: W. B. Saunders Company, 1940. $5.00.

The second edition of Dr. Major's textbook is even more attractive than the first. Its lively style, its wealth of historical allusions and its quotations from original and classic sources hold the reader's interest. The author is not afraid to append lists of bibliographic references to his chapters. A number of inaccuracies that marred the first edition have been corrected. The illustrations are abundant and good. The caption under Figure 373 on page 357, "Trophic changes in fingernails in pernicious anemia," should in the interest of accuracy be altered to "Spoon nails in anemia due to iron deficiency."

The March of Medicine. Edited by the Committee on Lectures to the Laity of the New York Academy of Medicine. 8°, cloth, 168 pp. New York: Columbia University Press, 1940. $2.00.

Recently the laity has shown much interest in the history of medicine, and the New York Academy of Medicine has been foremost in fostering this trend. The book is the fourth in the series, "Lectures to the Laity." The contributors, eminent in the field they have chosen to discuss, are Drs. Walter C. Alvarez, Sanford V. Larkey, Cecil K. Drinker, Charles G. Heyd, R. G. Hoskins and Karl A. Menninger. The preface is written by Dr. Malcolm Goodridge, president of the New York Academy of Medicine, who emphasizes the thesis, "Without the intelligent co-operation of the lay people, the full application of the advance in medical science will never be possible." The topics that make up these lectures are as follows: "From Folkways to Modern Medicine," "Health in Elizabethan England," "Not So Long Ago," "The Romance of Modern Surgery," "The Story of Insanity," and "The Cinderella of Medicine." This book may be read with equal interest and instruction by the layman, the medical student and the physician.